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A New Syndrome Combining Developmental Anomalies of the Eyelids, Eyebrows and Noseroot with Pigmentary Anomalies of the Iris and Head Hair and with Congenital Deafness; Dystopia canthi medialis et punctorum lacrimalium lateroversa, Hyperplasia supercilii medialis et radicis nasi, Heterochromia iridum totaliis sive partialis, Albinismus circumscriptus (leucismus, polioss) et Surditas congenita (surdimutitas) ..... *P. J. Waardenburg* 195

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Vol. 3 No. 3 *September 1951*

A New Syndrome Combining Developmental Anomalies of the Eyelids, Eyebrows and Nose Root with Pigmentary Defects of the Iris and Head Hair and with Congenital Deafness

Dystopia canthi medialis et punctorum lacrimalium lateroversa, Hyperplasia supercilii medialis et radicis nasi, Heterochromia iridum totalis sive partialis, Albinismus circumscriptus (leucismus, poliosis), et Surditas congenita (surdimutitas)

[Dedicated to J. van der Hoeve, Retired Professor of Ophthalmology, University of Leiden]

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FIRST OBSERVATIONS

A FEW years ago I was consulted in ophthalmological practice by an elderly tailor who, being a congenital deafmute, came to me accompanied by his niece. His complaints were varied; his vision had progressively worsened and he had suffered for many years from watering eyes. The case interested me particularly because of the presence of a distinct bilateral *dystopia canthi medialis lateroversa*.

Since its first description by van der Hoeve (1916) this anomaly has been recognized as a well defined clinical entity, consisting in a markedly increased distance between the inner angles of the eyelids (37–52 mm. or more in adults). This is accompanied by a correspondingly increased distance between the inferior lacrimal points; the latter are displaced laterally and are situated in front of the cornea, whereas in all normal variations of the interangular distance these lacrimal points are located between the medial corneal margin and the inner canthus, nearly opposite the plica semilunaris. The interpupillary and outer canthal distances lie within the normal variation range in this anomaly, so that there is a shortening of the palpebral fissures in the horizontal direction (*blepharophimosis*). All this leads to a normal visibility of the lateral part of the sclera, but a reduced visibility of the medial part. The anomaly may be accompanied by difficulties of lacrimal conduction and dacryocystitis. The anomaly differs from *hypertelorism* (lateral displacement of the eyes, eyelids, and orbits) in that the latter condition shows (1) no displacement of the lacrimal points nor reduced visibility of the nasal portion of the sclera, (2) no shortening of the palpebral fissures, and (3) abnormally increased distances between the pupils and outer canthi.

When there is a normal fold of the upper lid, it may occasionally happen that the region between this fold and the lid margin is broader on the nasal than on the temporal side, which imparts a characteristic facial expression (cf. fig. 2). This is produced by a sharp bending of the medial part of the upper lid margin, and it explains the fact that the upper lacrimal points seem to be normally situated. In reality they too are somewhat displaced, but because they project forward higher than usual, it is less striking. Both canaliculi lacrimales, the upper as well as the lower, are enlarged.

My patient showed also a dystopia of the lacrimal points, which, in this instance, were slightly everted, due to a tendency to ectropion of the lower lids (fig. 1). This combination of deafmutism and the anomaly of the eye region reminded me of the report by van der Hoeve (1916), who described the same anomaly in a pair of 14 year-old monozygotic twin girls (fig. 2), inmates of the institute for *deafmutes* at Groningen. I was suddenly compelled to wonder: could it be pure chance that three deafmutes in our country should display this rare abnormality of the eyelids?

I discussed this case at a meeting of the Dutch Ophthalmological Society in December, 1947, and this prompted a discussion remark by Dr. Goedbloed, oculist at the Hague (cf. Waardenburg, 1948). He had seen the same combination in a girl and procured for me the fourth Dutch case.

It was at this time that I took notice in Walsh's *Clinical Neuro-ophthalmology* (p. 492, fig. 176*B*) of a photograph of a brother and sister with "hypertelorism."

FIG. 1

FIG. 2

FIG. 1. Congenitally deaf 72 year-old male with dystopia canthi medialis lateroversa, dystopia of the lacrimal points, blepharophimosis, and iris dystrophy. The author's first case of the syndrome: probandus of Family Ro (Pedigree 1, *II-2*).

FIG. 2. Monozygotic twins concordant for congenital deafness and dystopia canthi medialis lateroversa, at the age of 14 years. Probandae of Families R-S and S-S (Pedigree 6, *II-6 left, II-7 right*). After van der Hoeve (1916) in *Klinische Monatsblätter für Augenheilkunde*, 56: 232.

FIG. 3. Patient of Dr. D. Klein, Geneva. After Klein (1950) in *Helvetica paediatrica acta*, 5: 40. Although the lid fissures at the inner angles were enlarged by operation, the inner canthal diameter is still abnormally large.

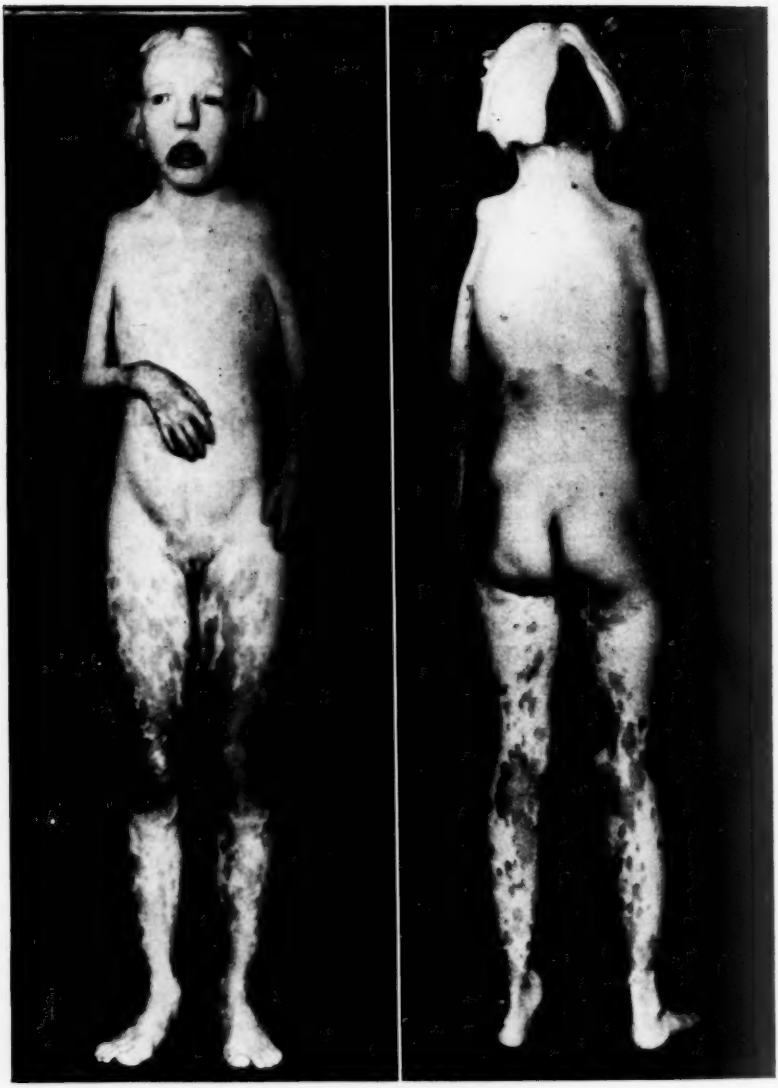


FIG. 4. Patient of Dr. D. Klein, Geneva. After Klein (1947) in *Archiv der Julius Klaus Stiftung*, 22: 337.

This diagnosis seemed questionable, for it was evident to me that the children showed dystopia lateroversa of the inner canthi, there being almost no sclera visible on the medial side. But what struck me especially was the statement that the girl, aged 3, was totally deaf, and that hearing in the boy, aged 5, was re-

tarded. In the text it is further noted that both children are intelligent, that the girl is a mute, and that both have patches of white hair exactly in the midline of the hair margin on the forehead; further, both show a faintly marked furrow in the forehead extending to the tip of the nose, and both have a nearly complete absence of the uvula. The visual acuity and ocular fundi were normal. The iris color is not mentioned; in the photograph it appears that the boy's irides are darker than the girl's and that both are isochromic. The inner and outer canthal distances are not recorded, so it is difficult to either agree or disagree with the diagnosis of hypertelorism; however, the photographs don't give the impression that the outer canthal distance exceeds much the normal distance.

In the following year, at the ophthalmic clinic of Prof. Franceschetti in Geneva, I had the opportunity to see a 10 year-old girl who had been studied by Dr. Klein (1947). A full description of this remarkable case has since been published (Klein, 1950). Shortly after birth the girl had been operated at the inner canthi for a disfiguring so-called *ankyloblepharon mediale* of the eyelids (fig. 3), and the narrow palpebral fissures had been widened for cosmetic reasons. I got the impression that the anomaly could not have represented a growing together nor a failure of opening of the lid margins, because such anomalies of a symmetric form at that part of the lids are unknown, but that it had been an extreme instance of the well-known lateral dystopia of the canthus. And, indeed, the lower puncta lacrimalia were dislocated in the direction of the corneae, as was clearly discerned even in the right eye in spite of a divergent squint. This girl was again a *deafmute* and showed not only a white forelock, as in the American cases, but a pronounced partial albinism of the entire body. The eyes were blue. In addition, there were deformities of the skull, the nose root, the palate, the teeth, and the jaws, an antimongoloid obliquity of the lid fissures, and a Rocher-Sheldon syndrome, the latter consisting of congenital amyoplasia of various skeletal muscle groups, multiple rigidities of the joints of the upper limbs, multiple dysplasias of the skeletal system, and webbing of both axillary folds and of the fingers of both hands (fig. 4).

A SEARCH AMONG INSTITUTIONALIZED DEAFMUTES

The coincidence of deafmutism and dystopia canthi medialis lateroversa in 4 Dutch, 2 American and one Swiss case, with concordance in uniovular twins and presence in a sister and brother, served as the starting point of a more extensive study carried out at 5 Dutch institutions for the deaf at Rotterdam, Amsterdam, Groningen, Voorburg, and St. Michielsgestel. To the directors of these institutes I wish to express here my gratitude for their kind assistance in my investigations, the results of which will now be presented in detail.

A total of 1050 individuals were examined. The majority were children, although at St. Michielsgestel there were perhaps, in addition, about 150 adults. A number of these were not deafmutes, but were hearing mutes with psychocerebral defects.

I was anxious to discover whether I should find cases of dystopia of the medial canthi and pigmentary anomalies among these deafmutes. As it developed, the search led not only to a confirmation of this association but indicated the existence of a hitherto unknown human syndrome, which may be described as a combination of 6 chief characteristics:

1) Lateral displacement of the medial canthi (*dystopia canthi medialis lateroversa*), combined with dystopia of the lacrimal puncta and blepharophimosis,

2) Prominent broad root of nose (*hyperplasia radicis nasi*),

3) Growing together of the eyebrows, with hypertrichosis of their medial portions (*hyperplasia supercilii medialis*),

4) White forelock, as a form of partial albinism (*leucismus pilorum* or *poliosis*),

5) *Heterochromia iridum totalis sive partialis*, and

6) Deafmutism or a somewhat incomplete degree of congenital deafness (*surditas congenita*).

Altogether, I found 13 cases of the eyelid anomaly among the 1050 inmates, and these individuals then became the probands for my family investigations. The syndrome proved to be hereditary, but, as is characteristic of genetic syndromes, the complex as a whole is frequently transmitted by individuals who do not show all of its component features. In fact, only a minority of the probands themselves exhibited all of the characteristics enumerated above, most of them showing only a few of them. In a later section the question of the varying degrees of penetrance of the component traits and other related matters will be discussed in detail. At this point I wish to make only a few preliminary remarks regarding the mode of inheritance of the syndrome and its bearing on the larger question of the genetics of congenital deafness in general.

In the beginning I expected to find a recessive inheritance, such as we are accustomed to look for in cases of deafmutism, and indeed, when I started with the examination of the relatives of the above-mentioned old tailor and the families of the first cases found at the institutes for the deaf, it seemed that this supposition might be right, because I could not find other affected persons in these families. But neither did I find consanguinity among the parents. In the entire material, including 34 cases of deafmutes belonging to 14 pedigrees, I have found not one instance of consanguinity among the parents of patients exhibiting the syndrome.

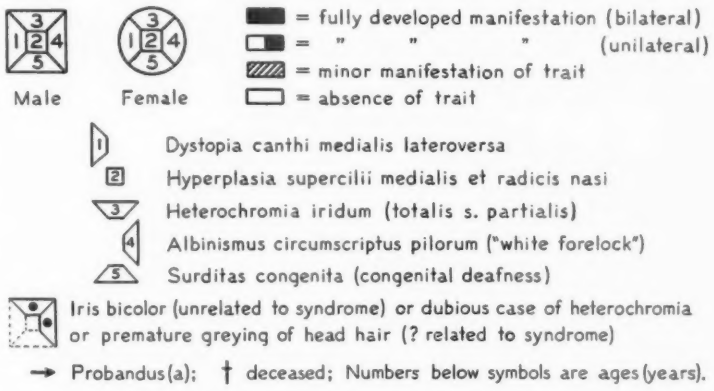
I therefore had to abandon the notion of recessive transmission in favor of dominant inheritance, and I did this the more readily as it soon became apparent on extending my studies that the syndrome repeated itself in successive generations. This seemed particularly interesting from the point of view of the genetics of deafmutism. For, if there really exist cases of "dominant" congenital deafness—meaning that this kind of deafness may manifest itself when inherited from only one parent, i.e., in heterozygotes having one normal allele—certain

puzzling facts in the literature on deafness might now find a plausible explanation.

For example, Grohmann (1939) described a mating of two deafmutes neither of whose parents were known to be related, but each of whom possessed deaf and deafmute relatives. This couple produced a normal daughter. Such events could in the past be explained by assuming 1) the existence of different recessive forms of deafness in the parents, 2) the presence of an "acquired" or non-hereditary deafness in one or both parents, or 3) a falsely represented paternity. However, the existence of an irregularly dominant form of congenital deafness would now permit a fourth alternative: 4) the presence in one or both parents of this dominant type of deafness instead of one of the more usual recessive forms. Even more significantly, perhaps, the new mode of transmission would assist in explaining those cases wherein two deafmute parents produce *both normal and deaf* children.

DESCRIPTION OF THE INVESTIGATED FAMILIES

The 14 investigated families are described in this section, beginning with the family of the elderly tailor who first drew my attention to the syndrome. In the pedigree charts, the following symbols are used:


3
1 2 4
5
Male
Female
= fully developed manifestation (bilateral)
= " " " (unilateral)
= minor manifestation of trait
= absence of trait
1 Dystopia canthi medialis lateroversa
2 Hyperplasia supercilii medialis et radicis nasi
3 Heterochromia iridum (totalis s. partialis)
4 Albinismus circumscriptus pilorum ("white forelock")
5 Surditas congenita (congenital deafness)
Iris bicolor (unrelated to syndrome) or dubious case of heterochromia or premature greying of head hair (? related to syndrome)
→ Probandus(a); † deceased; Numbers below symbols are ages (years).

In the clinical descriptions, the distances between (*a*) the inner or medial canthi, (*b*) the pupillary centers, and (*c*) the outer or lateral canthi are recorded for brevity's sake in a formula: *a-b-c*, each diameter or distance being measured in millimeters. Collectively these measurements will be referred to as the "interocular dimensions."

For the inner canthal diameter (*a*), the normal range of variation in adults of mixed European populations is 24–37 mm. in women, with a peak frequency at 32–33 mm.; in men, 26–39 mm., with a peak at 33–34 mm.

For the interpupillary distance (*b*), the range is 54–72 mm., with a mean of 62.67, in women; and 58–75 mm., with a mean of 65.33, in men.

For the outer canthal diameter (*c*), the range is 74–92 mm., with a modal value of 83 mm. in women; and 77–96 mm. with a mode of 87 mm. in men.

There is no sharp line of demarcation between normal broad face and hypertelorism; they overlap each other. The interocular dimensions for hypertelorism, expressed as ranges, are as follows: a = 42–45 mm., b = 72–76 mm., c = 100 mm. or more.

All interocular dimensions were measured by me in the usual way, with a ruler held horizontally at the nose root. For the real air distances of the inner and outer canthi no difficulties arise, because these are about the same as their rectangular projections at the horizontal imaginary airline represented by the ruler.

A slight difficulty arises in measuring the lengths of the lid fissures. The outer canthi are generally situated more or less behind (posterior to) the inner canthi, and the lid margins form a curved line over the eyes. One may measure the length of the lid fissures in two ways, either by projection on a ruler held obliquely at the nose root, parallel to the canthi, or by following the lid curvature with a flexible tape. In both cases, and especially when using the latter method (which is always noted in the text), the lengths of the fissures are found to be bigger than those measured by projection on a ruler held at the nose. Slight discrepancies between the outer canthal distances as cited in this paper and the sums of the inner canthal diameter and the two fissure lengths may be due to this fact and to inevitable errors of measurement.

Pedigree 1. (Family Ro, Fig. 5)

II-2. (The *probandus*, H. Ro., Fig. 1). This 72 year-old bachelor tailor was congenitally deaf and suffered from bilateral glaucoma simplex. There was also a peculiar form of peripupillary *iris atrophy*, unlike the usual secondary types seen in glaucoma, and producing

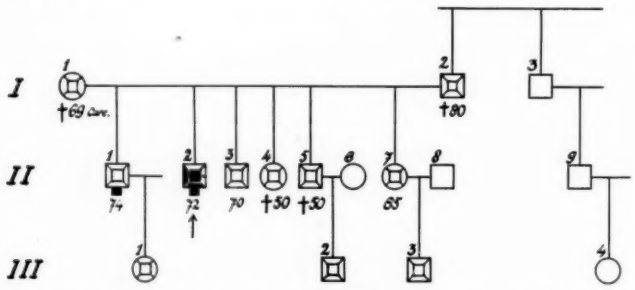


Fig. 5. Pedigree 1, Family Ro. Black rectangles attached to the symbols for *II-1* and *II-2* denote glaucoma simplex, regarded as a complication unrelated to syndrome.

irregularly shaped, rather wide, incontractible pupils. It is difficult to decide in this case whether the whole iris dystrophy is a primary one, or whether it was due in part to the increased intraocular tension, the latter also producing a sphincter paralysis. The irides are steel-blue and isochromic, with a very thin flat structure and with practically no difference between the two iris circles. Owing to the patient's baldness and poor memory, I could not discover whether a white forelock had been present in youth. In a portrait taken at the age of 42 his *head hair* appears *nearly white*, but his eyebrows—which were grown together—and moustache were dark-colored. The eyebrows and lashes now reveal some white hairs among darker ones, and there are some inconspicuous vitiligoid skin spots in the neighborhood of the eyes, but these features cannot be regarded as evidence of partial albinism in

a man of this age. The nose has an irregular contour and deviates somewhat to the right. The interocular distances are: 46.5-67.5-89.0. The inferior lacrimal puncta are 57 mm. apart, each situated 1.5 mm. temporally from the corneal limbus. Palpebral fissures measure in curvature only 23 mm. There was a chronic conjunctivitis, with ectropion and epiphora and a right-sided slight dacryocystitis—symptoms occasionally found in other comparable cases. For further notes on this case see Waardenburg (1948).

II-1, *II-7*, *II-8*, *III-1*, *III-2*, and *III-4* were examined; none showed dystopia canthi medialis or other features of the syndrome. The proband's eldest brother, *II-1*, also suffered from glaucoma, *but without iris dystrophy*, and has been operated by me bilaterally. His interocular dimensions were: 33-64-89. In all other members shown in fig. 5, including *I-1* and *I-2*, who had died at ages of 69 and 80, resp., the syndrome could be excluded from portraits. The entire family has steel-grey or blue irides, and all measured interocular distances were normal.

Comment: In the light of many other families showing dominant inheritance of the syndrome, this solitary case is perhaps best viewed as an instance of new mutation.

PEDIGREE 2. (FAMILY NA, FIG. 7)

II-1. (The *probandus*, Gerrit Na., Fig. 6). This 63 year-old deafmute was discovered in my examinations at St. Michielsgestel. He has the anomaly of the inner eye angles and of the nose root. I am uncertain whether the eyebrow anomaly was present, because at that

FIG. 6. Congenitally deaf 63 year-old male, with dystopia canthorum and heterochromia iridum. Probandus of Family Na (Pedigree 2, *II-1*).

time this feature of the syndrome had not been drawn to my attention. He had a *heterochromia iridum*, consisting of a greenish right iris with a brown lesser circle and a light blue left iris. The palpebral fissures measured 21 mm. O.U. His head is now bald; whether a strand of white hairs had been present could not be established. Interocular distances: 47-68-88.

II-2, the proband's twin brother, had died before school age. There were no photographs available, and nothing could be learned through the parents or relatives about the child's appearance. His hearing was reported as normal.

II-3, a brother, aged 62, had been operated for bilateral acute glaucoma. Interocular distances: 37-71-102—this means a kind of *hypertelorism*. The irides were blue, with a trace

of yellow. The lacrimal points were normally situated. The inner canthal distance (37 mm.) is normal, but somewhat about average. This man was bald, like the probandus. His wife, *II-4*, and four daughters were examined and found free of all symptoms of the syndrome.

II-5, another brother, aged 60, was bald and had about the same eye color as *II-3*. Interocular distances: 36-64-85. The eyelids appeared entirely normal, although the fissures were a bit small. His wife *II-6*, a son *III-5*, and daughter *III-6* were normal, except for a rather pronounced myopic astigmatism in *III-5*, but the younger sons presented some difficulties for diagnosis of the syndrome. *III-7* suffered from horizontal nystagmus and high myopia (13 diopters O.U.) and had very broad nasal bones as is characteristic of the syndrome. His irides were isochromatic, of an olive-brown trabecular type. The lacrimal points are normally situated. Interocular distances: 39-64-90. The first figure exceeds the normal range; the others do not, but they can be interpreted as leaning toward hypertelorism as well as to dystopia canthorum. The youngest son, *III-8*, has normally situated lacrimal points, with interocular distances: 39.5-70.0-102.0. The irides are blue, with some admixture of yellow. The palpebral fissures have an antimongoloid direction. The eyebrows are heavy and somewhat grown together over the high, broad, nasal root. The impression gained

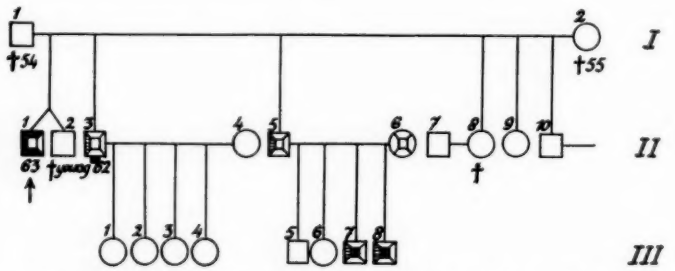


FIG. 7. Pedigree 2, Family Na. Black rectangle attached to symbol for *II-3* denotes glaucoma. *II-3* and *III-8* have a tendency to hypertelorism.

is that this son shows a slight or abortive form of dystopia canthi medialis combined with ***hypertelorism.***

II-8 and *II-9* were normal, judging from photographs and family history. *II-10* and his 11 children proved to be normal by personal examination.

Comment: Since hypertelorism is generally associated with normal or enlarged lid fissures, and perhaps also with enlarged laterally displaced orbits, whereas dystopia canthorum of the present syndrome produces narrow lid fissures, the question arises as to whether both characteristics may not be present in this family, tending to abolish one another.

PEDIGREE 3. (FAMILY JA, FIG. 8)

IV-3. (The *probandus*, Ferdi J., Fig. 8). This 8 year-old deaf boy was found at the institute at Voorburg. He has the full syndrome except for the white forelock. *Heterochromia iridum* was present in the form of a blue right eye and a greenish left eye, the latter having an olive-brown peripupillary ring with radiations of the same color to the periphery. Palpebral fissures measured 20.5 mm. O.D. and 21.0 mm. O.S. Interocular dimensions: 38-55-78. The following relatives were examined:

IV-1, a 14 year-old brother, lacking the syndrome, has fair hair and greyish irides.

IV-2, an 11 year-old sister, also normal, has an iris color similar to the father, *III-1*.

IV-4, a 5 year-old sister, has fair hair and no definite signs of the syndrome. The iris color is somewhat darker than in the father, with the right iris very slightly darker than the left.

IV-5, a 3 year-old sister, has fair hair and iris color like her mother's, but without nevi.

III-1, the father (A. J.), 44 years of age, has irides with an orange peripupillary ring and a greenish periphery. Interocular dimensions: 35-67-93.

III-2, the mother (H.G.J.v.A.), aged 45, differs but little from her husband in iris pigmentation; the peripupillary ring is more olive-yellow and the periphery shows some darker nevi. Interocular dimensions: 29-57-83. She is an only child and acquired deafness at age 15 at menarchy.

All portraits of the various ancestors and paternal aunts and uncles show normal configurations in the eye region. One maternal uncle (*II-4*) became hard of hearing at a late age.

Comment: This isolated case again leads me to assume the occurrence of mutation.

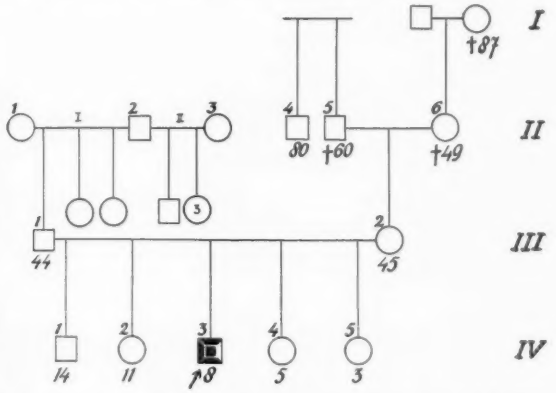


FIG. 8. Pedigree 3, Family Ja, and 8 year-old deafmute probandus (*IV-3*) with typical features of the syndrome.

PEDIGREE 4. (FAMILY BO, FIG. 9)

III-3. (The *probandus*, Jan. B.). This 17 year-old deaf boy worked in a carpenter's shop at the institute in Groningen. On examination it was clear that he did not show dystopia canthorum. The eyelids and fissures were of normal shape, but I was immediately struck by the presence of a *broad patch of white hair* in the front of the forehead and by an evident, though slight, *heterochromia iridum*. The right iris was blue with white trabeculae. The left eye was blue with a yellowish cast, the yellow pigment being concentrated near the pupil and along the trabeculae, especially in the lower half of the iris. The *eyebrows* were *confluent*, the *nose root high*, but rather narrow. Visual acuity and refraction findings were normal. Interocular dimensions: 31.5-61-83.

III-1, a half-sister of the probandus, is normal.

III-2, a half-brother, was personally examined and found normal. The eyebrows are heavy but not grown together, and the nose bridge is narrow. Iris color is blue, with a yellow ring.

III-4, a full brother, died at age 10, was probably normal.

III-5, a full sister, was personally examined and found normal.

I was unable to investigate this family further myself, but an indebted to Dr. Krooneberg for the following information on other members of the family: The probandus' father (*II-4*) had a narrow high nose bridge and blue eyes, without any anomaly. The mother (*II-5*)

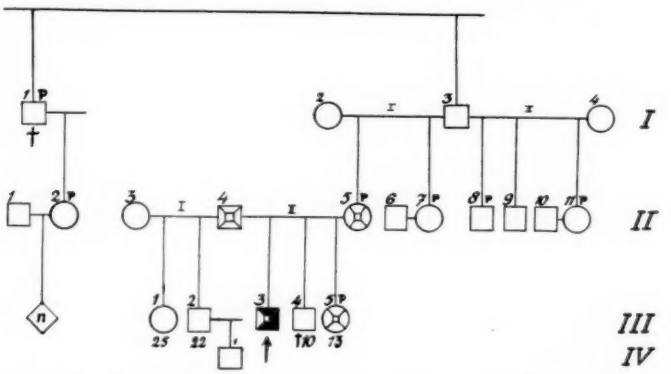


FIG. 9. Pedigree 4, Family Bo. The eyelid anomaly is absent. Letter *P* denotes *mandibular prognathism.*

had grey irides with a brown peripupillary ring; the only anomaly consisted in a corneal macula of the left eye. Neither parent showed a white forelock. The mother's family is characterized by an apparently dominantly inherited mandibular prognathism of the Habsburg type (fig. 9).

Comment: In this family we are probably again dealing with a newly arisen mutation in the probandus, which in this case has the peculiarity of having produced in him all features of the syndrome excepting dystopia canthorum and the anomaly of the eyebrows and nose root.

FIG. 10. Probandi of Family Dru (Pedigree 5, *V-3* and *V-6*), 17 year-old sister and 10 year-old brother, both deaf and showing all other features of syndrome excepting white forelock.

PEDIGREE 5. (FAMILY DRU, FIG. 11)

In this family there are two probandi, a 17 year-old girl (*V-3*) and her 10 year-old brother (*V-6*), both deafmutes and inmates of the institute at St. Michielsgestel. In addition, congenital deafness occurs in another brother (*V-4*) and in a cousin (*IV-10*).

V-3. (*Probanda*, Johanna D., Fig. 10, *left*). This 17 year-old deaf girl has dark brown irides, but the right iris has a blue sector at 6 o'clock. An irregular depigmented skin spot is located on the right forearm. The lacrimal points are just opposite the medial corneal limbi. The eyebrows are grown together over a high broad nose root. Palpebral fissures measure 22.5 mm. O.D. and >23 mm. O.S. Interocular dimensions: 44-64-88.

V-6. (*Probandus*, Albert D., Fig. 10, *right*). This 10 year-old boy, a born deafmute, has a blue right eye and a light brown left eye. The inferior lacrimal points lie opposite the corneae. Lid fissures measure 22 mm. O.D., 23 mm. O.S. Interocular dimensions: 41-60-82.

V-1. A normal brother, Honoré D., aged 22, has brown eyes. Interocular dimensions: 33.5-63.5-86. Palpebral fissure widths: 26.5 mm. O.D., 27 mm. O.S.

V-2. This brother, August D., aged 20, has olive brown eyes, a broad high nose bridge, and dystopia canthorum (dimensions: 43-63.5-86). The eyebrows are confluent.

V-4. This 14 year-old brother, Roger D., has congenital hardness of hearing bilaterally. The irides are olive-brown, but there is a narrow (1 mm.) sector of blue extending from pupil to limbus at 2 o'clock in both eyes. Interocular dimensions: 38-61-80. The eyebrows are grown together.

V-5. A sister, Paula D., aged 13, is quite normal. She has fair hair and the irides are blue, with some yellow. Interocular dimensions: 35-63-85.

V-7. This 6 year-old brother, Paul D., has the eyebrow and eyelid anomalies and a distinct *heterochromia iridum*. The right iris is diffusely light brown; the left iris is bright blue. The nose root is broad, but not very prominent. Interocular dimensions: 43-57-82. Palpebral fissures measure 20 mm. O.D., 21 mm. O.S.

V-8. This 3½ year-old sister, Hilda D., has the eyelid anomaly in a very marked way (dimensions: 37-56-76). Lid fissures measure 20.5 mm. O.U. The caruncles are small. The eyes are dark brown, isochromic. The head hair is dark.

IV-3. The father of the probandi, 48 years of age, had been operated for cataracts in each eye, a disease not known in other members of his family. I found him quite normal in respect to the syndrome. The irides are brown. Interocular dimensions: 29-65-90. Palpebral fissures are rather large, 30.5 mm. O.D., 31 mm. O.S.

IV-4. The 48 year-old mother Leonie D.-S. shows the anomalies of the nose root, eyebrows and eyelids. Interocular dimensions: 43-64.5-87. Caruncles are moderately enlarged. She has brown eyes which are greenish in areas between the brown radiations. The head hair is dark. Her nose shows a deviation to the right side. Of this woman's sibs I was able to examine only a brother Alphons, *IV-1*, who exhibited the eyelid anomaly and the high broad nose root, and one sister, Martha, *IV-8*, who was quite normal and had brown irides. Pictures of the other 4 sisters revealed no abnormalities.

III-3, the maternal grandfather, August S., aged 77, was examined and showed the eyelid anomaly. He suffered from epiphora and pterygium nasale, O.S. The caruncles were moderately enlarged. The eyebrows contained many white hairs and were grown together slightly. The irides were brown near the pupils and grey toward the periphery. Interocular dimensions: 44-63-82. Lid fissures, 21 mm. O.U. The nose root was moderately high and rather narrow. This man said he could well recall the narrow lid fissures and broad nose root in his father, Theophyl S. (*II-1*), and in his grandfather (*I-1*). Also, his sister, Josephine (*III-2*), was described as having one blue eye and one dark eye in addition to the other anomalies; she had no children.

I-1, the oldest known ancestor with dystopia canthorum, also had an afflicted daughter,

Mina S., *II-5*, who transmitted the anomaly in two additional lines, once through her illegitimate daugher Hermance (*III-6*), and once through her son, Alphons (*III-7*). The daughter (*III-6*), has one brown and one blue eye. She has transmitted the syndrome to 5 descendents in 2 generations, as follows:

IV-9, a daughter, Maria R., aged 52, is quite normal. Interocular dimensions: 32-62-84.

IV-10, Alphons R., an unmarried son, aged 50, is a *congenital deafmute*. The irides are whitish-blue with a *very hypoplastic stroma* and visible pigment layer. The eyebrows are grown together. Palpebral fissures in curvature measure 24 mm. O.D., 25 mm. O.S.; in projection, 20 mm. O.U. Interocular dimensions: 42-65-82. The nose root is broad and very high.

IV-12, the younger daughter, Bertha R., aged 47, has *heterochromic irides* like her mother. The right eye has a diffuse brown color, while the left iris is blue, with a *very hypoplastic stroma*. The left pupil is much wider than the right; both pupils react to light and there is no difference in the widths of the lid fissures (measuring, in curvature, 23 mm. O.D., 22.5 mm. O.S.) accompanying the *anisocoria*. The nose root is very prominent, the eyebrows

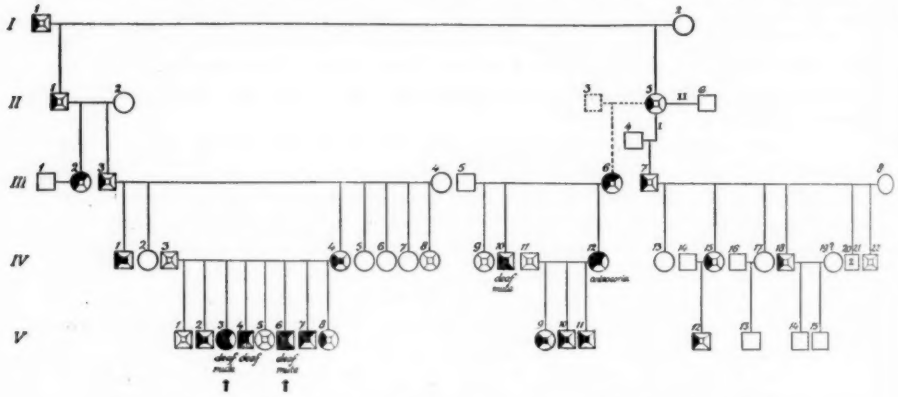


FIG. 11. Pedigree 5, Family Dru. (For explanation of symbols see p. 201)

grown together. The right caruncle is normal, the left slightly increased in size. Interocular dimensions: 44-64-85. This woman's husband (*IV-11*) is quite normal (interocular dimensions: 29-60-84) and has blue eyes with a trace of yellow. Her 3 children all possess the eyelid and nose deformities, without heterochromia or deafness. Their eye colors vary between that of the father and that of the darker eye of the mother, being olive-brown with a greyish periphery. Only two were available for examination: the older boy (*V-10*), aged 11, has interocular measurements of 46-65-87; the younger (*V-11*), aged 8, has measurements of 42.5-53.5-78 and the lid fissures measure 20 mm. O.D., 18 mm. O.S.

III-7's descendants who possess the syndrome, namely *IV-15*, *IV-18*, and *V-12*, all exhibit the dystopia and high nose bridge, and perhaps also the hyperplastic eyebrows (at this stage of the study I did not systematically examine for this feature).

I observed the caruncles in most of the affected individuals and found them normal or very little increased in volume.

Comment: This family clearly demonstrates the dominant inheritance of the syndrome through 5 generations, of which 3 were personally examined. Most consistently manifested

are the anomalies of the eyelids and of the nose bridge and eyebrows, but there are also 7 cases of heterochromia iridum and 4 cases of congenital deafness. One affected member showed anisocoria, and one deafmute displayed a thin iris stroma, as did also a normally hearing sister who had the syndrome. A white hairlock is not present in this kindred, so it is doubtful whether the depigmented skin area in one case has any significance. It will be noticed that the heterochromia in different affected individuals may be either partial or total.

Pedigree 6. (Families R.S. and S.S., Fig. 12)

In this family my probandae were the deafmute uniovular twins who, at the age of 14, were described by van der Hoeve in 1916. Both girls had grown up and had married deafmutes with whom they had made acquaintance at the institute at Groningen.

II-6 and *II-7*. (*Twin probandae*, Fig. 2), now 49 years old. The first-born of the twins (*II-6*, Jantje R.-S.) and her husband were examined by myself. I am indebted to Dr. Hijmans at Rotterdam for his kind assistance in examining the other twin (*II-7*, Boukje) and her sons living there. It is improbable that these twins had a distinct white forelock in their youth, but it is a fact that *both turned grey at an early age*, and have been for several

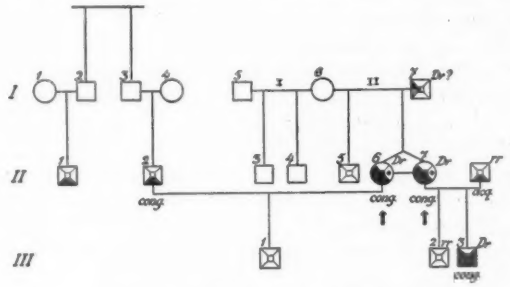


Fig. 12. Pedigree 6, Families R-S and S-S

years quite white. The irides are bright blue, with a *thin stroma*. The anomaly of the eye region is very marked in both. The interocular dimensions are 44-58-83 in Jantje and 42-57-82 in Boukje.[2] Both have the same degree of marked hypermetropia with slight astigmatism.

II-2. Husband of *II-6* (Jantje). This man is a congenital deafmute, and has a normal configuration of the nose and eyelids. A cousin of his (*II-1*) is also a deafmute, but it is uncertain whether this is an acquired or hereditary form of deafness. In any case, this first deaf couple have a normal son (*III-1*), who is a mariner. So it is clear that in case of a hereditary defect in both, the underlying genes must be different ones.

[2] At the age of 14 the twins' interocular dimensions were recorded by van der Hoeve (1916) as follows: inner canthal diameter 41 mm., outer canthal diameter 85 mm. in both girls; the interpupillary distances were not recorded, but the palpebral fissures were measured to be 22 mm. o.u. in both twins. Evidently the latter figures were added to the inner canthal diameters to give the outer canthal diameters, or else he measured the outer canthi by following the lid curvatures. It may be that the shorter distances for the outer canthi found independently by Dr. Hijmans and myself result from the fact that we measured these diameters by projection at the airline. But, in addition to this fact and the possibilities of errors in measurement, the discrepancy may be in part due to an actual shortening of the lid fissures with advancing age.

II-8. Husband of *II-7* (Boukje). It is certain that this man has an acquired deafmutism. This couple have two sons:

III-2, the elder son, aged 22, is normal (dimensions: 30-62-82), but *III-3*, the younger son, aged 19, is again a deafmute with other manifestations of the syndrome. He has no trace of hearing, and shows a *distinct white forelock*. The palpebral fissures are narrow; interocular dimensions: 45-62-97. The irides are isochromic, light blue. His vision is not good; his refraction is hypermetropic-astigmatic.

I-7, the father of the twins, is dead. He showed dystopia canthorum in the right eye only, judging from an enlarged portrait. The iris color is light in both eyes. The twins were born in a second marriage of the mother. They have one normal full brother (*II-5*) and 2 normal half brothers (*II-3*, *II-4*).

Comment: Here again we see a dominant inheritance of the syndrome, with deafmutism in 2 consecutive generations. In this family heterochromia was impossible, as all affected members showed thin irides without stromal pigmentation. The question is also raised whether early greying of the hair in the twins and white forelock in one son may not be equivalent components of the syndrome.

Pedigree 7. (Family Schu, Fig. 13)

III-7. (The *probandus*, Gerard S., Fig. 13). This 18 year-old congenital deafmute is the fourth child in a family of 4 from the North of the Netherlands, and is now an inmate at St. Michielsgestel. His appearance immediately convinced me that he has the syndrome. There is no heterochromia or white streak of hair, but the nose root is prominent, the eyebrows grown together, and the lid fissures are very narrow (22 mm. o.u.). Interocular dimensions: 42-63-85. The irides are bright blue, with a thin stroma.

III-4, the eldest brother, aged 23, is affected. The irides are blue, with pale yellow trabecles. Lid fissures measure 22 mm. o.u., with interocular dimensions: 47-67-87. The nose root is high and eyebrows grown together.

III-5, a 22 year-old sister, is normal. Irides are blue, with thin stroma. Interocular dimensions: 32-61-84.

III-6, an unexamined brother, is normal according to family information and a good portrait.

III-8, a 16 year-old sister, also normal. Irides are blue, with thin stroma. Palpebral fissures measure 27.5 mm. o.d., 27 mm. o.s. Interocular dimensions: 31-56.5-82.

III-9, a 13 year-old sister, has irides of greenish hue (yellow spread over entire surface). No signs of syndrome. Interocular dimensions: 32-61-81.

III-10, the youngest sister, aged 11, is affected. Irides are diffuse brown, trabecular. The nose root is high and eyebrows are somewhat grown together. Interocular dimensions: 37-54.5-78.

II-10, the mother, aged 45, has grey irides with some brown nevi and some yellow pigment. The lid fissures are rather narrow (25 mm. o.d., 27 mm. o.s.) but on the whole there is no indication of the syndrome. The nose bridge is not prominent. Interocular dimensions: 31-57-77. Portraits of this woman's relatives reveal no signs of the syndrome.

II-4, the father, aged 49, is blue-eyed, and also lacks definite signs of the syndrome. The nose and lids appear normal. Interocular dimensions: 34-66-88. There are a few grey hairs in the middle of the forehead, but his age permits this distribution.

Comment: When we ask which of the parents transmitted the syndrome to 3 of the 7 children in this family, it is difficult to supply the answer. Neither parent shows the syndrome, nor is there any known blood relationship between them. Comparing portraits of the various paternal and maternal relatives I am now inclined to assume a transmission

through the paternal line, for the mother's relatives show nothing abnormal whereas the portraits suggest a bilateral defect of the eyelids in one paternal aunt (*II-5*) and a unilateral (right-sided) defect in an uncle (*II-3*) and in the paternal grandmother (*I-2*). Presumably we are dealing here with reduced penetrance of the dystopia canthorum feature in other persons of this kindred not examined by me. However, should this prove to be incorrect,

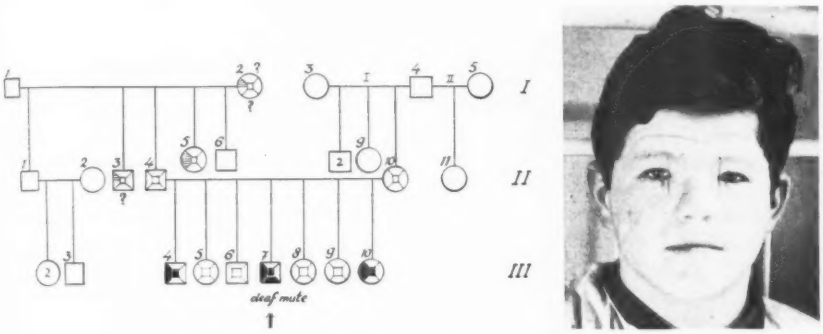


FIG. 13. Pedigree 7, Family Schu, and 18 year-old deafmute probandus (*III-7*) showing dystopia canthorum and hyperplasia radicis nasi.

and should the traits found in the father and his relatives prove accidental and of no significance as indicators of the syndrome, then the only assumption consistent with dominant inheritance which one could make would be to assume somatic mutation occurring in a diploid cell from which later many generative cells derive; the mutant gene could thus come to be transmitted to more than one affected child.

PEDIGREE 8. (FAMILY KO-SP, FIG. 14)

III-6. (*Probandus*, Anton K.). This 17 year-old deafmute was referred to me by the director of the institute at Rotterdam. Other than total congenital deafness he showed only a *heterochromia iridum* (diffuse olive-brown with brown Wölfflin points at the periphery O.D., bright blue with white Wölfflin points O.S.). The skin shows an abundance of freckles. Both eyes show a similar degree of fundus flavus, but the discs have small pigment borders. There is no white forelock. The eyebrows, nose and eyelids are normal (interocular dimensions: 33-57-83). I was able to examine several relatives of this proband:

II-11, the father, Cornelis K., aged 49, is a congenital deafmute, who, according to his own account, lacks bone conduction in both ears. He has normal eyelid configuration (inner canthal diam., 32 mm.; outer canthal diam., 84 mm.), but he had become white-haired in his early twenties. His left eye had been enucleated following an accident, but according to his statement, the iris had been olive-brown with a blue sector in the upper half, exactly as in the right iris which I examined. His refraction is 4 D. hypermetropia. Besides the *bilateral iris bicolor*, deafness, and premature whitening, there were no other abnormalities found. He is the third of 4 children by a second marriage of his father, and has 4 normal half-sibs. So far as he knows, he and a full brother (*II-7*) are the first cases of deafness in his father's family.

II-7, Ahazverus K., a paternal uncle, aged 56, has total congenital deafness of the right ear only. The drums and bone conduction are normal. There is a distinct *heterochromia*

iridum. The right iris is the darker one, being olive-brown near the pupil and lighter in the intermediate zone between pupil and periphery; the left iris is blue with white lines, and is not diaphanic. Vision is normal, O.U., with emmetropia. He has normal, rather thin eyebrows, normal inner canthi, nose root and puncta lacrimalia. Interocular dimensions: 31-66-87. He never possessed a white forelock. He is married but without children.

I-2 and *I-3*, the parents of the proband's father, were both dead, so I cannot give any first-hand information, but in photographs *I-2* appears normal in the eye region with a light iris color O.U., as was confirmed by his descendants. It is improbable that he transmitted the syndrome because 4 children by his first marriage and all their children are normal. No heterochromia could be recalled in the grandmother, *I-3;* she was said to have brown irides. I assume all features of the syndrome to be absent in this pair. Of the grandmother's sibs I could examine one sister, *I-4:*

I-4, female, aged 87, was practically blind. Her left eye had been operated for cataract without success and now shows a bullous dystrophy of the cornea. The right eye shows advanced cataract and a broad arcus senilis. The iris color is difficult to judge, but appears to be diffuse brown O.U. There is no anomaly of the canthi (dimensions: 30-56-78), but

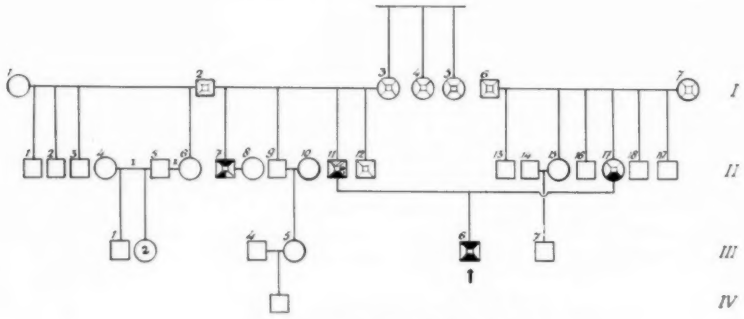


FIG. 14. Pedigree 8, Family Ko-Sp

there is a peculiar facial type in this family. *I-4*, and her sisters *I-3* and *I-5*, as well as other relatives, have eyes lying deep in the orbits with a kind of proptosis of the upper lids. They have a high lid furrow and the upper orbital margin forms a high round arch, the skin bending sharply inward, producing a kind of cavity. These people have transversely small lid fissures, which they close tightly.

II-17, the mother, Christina K.-S. aged 48, is also a congenital deafmute, the only member of her family known to be so afflicted. Her parents are not known to be related, nor is she of any known relationship to her husband *II-11*. It is not certain whether her deafness was congenital and of a genetic type or whether it was an early acquired form. She has light hair, dark eyebrows, blue irides, normal eyelids (dimensions: 31-57-81), and nothing extraordinary. The blue irides show fine yellowish-white radial lines and small Wölfflin points of the same color at the periphery. Her mother showed a high broad nose and—like two of her sons—rather small lid fissures with photophobia.

Comment: In this family the only symptoms inherited are heterochromia iridum and a unilateral deafness or deafmutism which appears to be transmitted from father to son. There is no proof that the mother belongs to the same genotype, so these features of the syndrome are probably manifesting themselves in heterozygotes.

PEDIGREE 9. (FAMILY VI, FIG. 15)

IV-5. (*Probandus*, Jan V., Fig. 15). This 14 year-old deafmute boy was found at the asylum at Voorburg. He had the eyelid defect, with palpebral fissures measuring 24 mm. O.U. The interocular dimensions, 46-69-94, show that the dystopia is here combined with a tendency to hypertelorism. The irides are greyish-blue. The eyebrows are grown together and there are a small number of white hairs in the midline on the forehead.

IV-6, a sister, Mintje V., aged 12, is quite normal. The interocular dimensions of 33-61-93 show the same tendency to hypertelorism. Lid fissures measure 30 mm. O.U. The irides are blue with some peripupillary yellow.

III-11, the mother, Hieke V.-T., aged 42, has normal eyes, with interocular dimensions: 29-62.5-84. Lid fissures measure 27.5 mm. O.U. The irides are blue with peripupillary olive-yellow.

III-10, the father, Bouke V., aged 42, shows the syndrome, with typical anomalies of the nose root, eyebrows and eyelids. Interocular dimensions: 51.5-68.5-92 (tendency to hypertelorism). Lid fissures measure 24 mm. O.D., 23 mm. O.S. The lacrimal points are situated

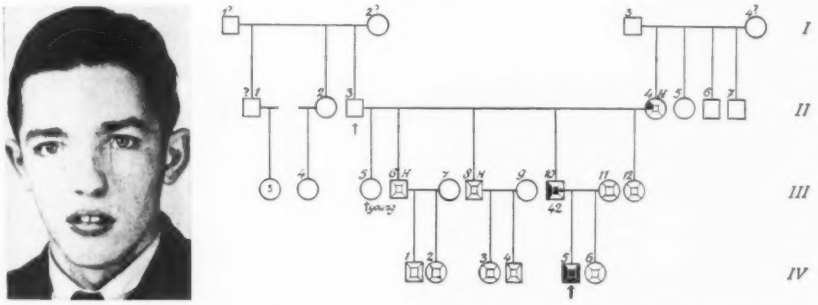


FIG. 15. Pedigree 9, Family VI, and 14 year-old deafmute probandus (*IV-5*) with typical anomaly of the eyelids, delicate white forelock, and other features of the syndrome. Letter *H* denotes *hypsicephalia*.

in front of the corneae, as in the probandus. He has suffered from *dacryocystitis*. Iris color is bright blue, with thin stroma. The head hair *turned grey before marriage*.

Of the father's sibs, all of whom are light eyed, *III-5* died young; *III-6* and *III-8* show *hypsicephalia* like their mother (*II-4*); *III-12* acquired partial deafness in one ear at an advanced age. Their father (*II-3*) was dead, but I was able to examine the mother:

II-4, the proband's paternal grandmother, aged 71, showed a pronounced *hypsicephalia* or unusually high forehead and skull. The lid fissures are narrow (22 mm. O.D., 21 mm. O.S.). Interocular dimensions: 37-58-78. The inferior lacrimal point O.D. faced the inner part of the cornea. The left eye showed a nebula corneae and some divergent strabismus. The iris color is bluish-grey with a small yellowish ring. The nose root is medium high. One gains the impression that the dystopia canthorum is here manifested only on the right side, and the same appearance is evident in a childhood portrait. It may be that the hypsicephalia is here counteracting the dystopia.

One can see from a large (nearly life size) portrait that the great-grandfather *I-3* was normal (interocular dimensions taken from the portrait: 30-55-87). His eyes were said to have been light-colored. The status of his wife (*I-4*) could not be established, but one could judge from photographs that her sibs (*I-5*, *I-6* and *I-7*) were probably normal.

The father's father (*II-3*) and his sister showed no abnormalities.

Comment: This family shows inheritance of the syndrome through 2, and perhaps 3, generations, but the component of heterochromia makes no appearance in any individual. This family is a Friesian stock with no cases having darker eye colors, which explains the absence of heterochromia.

Pedigree 10. (Family Kr-Gi, Fig. 17)

III-40. (*Probanda*, Therese K., Fig. 16). This 16-year-old girl, a congenital deafmute at the institution at St. Michielsgestel, showed the *complete syndrome*. The lid fissures measured in curvature 23 mm. o.u.; the interocular dimensions were 43-62-85. There is a marked *facial asymmetry*. The eyebrow anomaly is present, but the right eye and right eyebrow are about 5 mm. higher than those on the left. The nasalia are broad and high, and the nose deviates markedly to the left. The head hair is medium brown, with a typical "white blaze." There is a heterochromia iridum, the left half of the right iris is brownish from 1 to 7 o'clock with two darker sectors at 2 and at 6 o'clock; the left iris is whitish-blue. Visual acuity is normal, o.u. She has some irregular spots of depigmentation on the back and on the lateral aspect of the left forearm, a kind of indistinct *localized leucism*. In a sibship of 11 she is the only one who is a deafmute.

Fig. 16. Probanda (*III-40*) of Pedigree 10 (Family Kr-Gi) and her 10 year-old brother (*III-43*), both showing all features of the syndrome, excepting deafness, absent in the boy.

III-33, the eldest sister, Willemien, aged 27, is a nurse who has the eyebrow and eye anomalies (interocular dimensions: 43-66-88), the prominent nose root, dark hair containing a *white strain*, and *heterochromia iridum* (the right iris is bright blue, the left brown). There is no refraction anomaly or other eye defect. The breasts are of equal volume and pigmentation, and there are no signs of dysraphia except for an *increased arm span* (176 cm.) compared to standing height (166 cm.).

III-34, a sister, Henrica, aged 26, is quite normal. Interocular dimensions: 33-62-93. The irides are isochromic, whitish-blue. There is a slight esophoria and hypermetropia.

III-35, a brother, Bernard, aged 25, is normal (interocular dimensions: 32-63-93), with brown irides.

III-36, a brother, Johan, aged 24, has the syndrome. He has brown eyes and dark hair with scattered tufts of white. Lid fissures: 22 mm. O.D., 23 mm. O.S. Interocular dimensions: 43-68-96.

III-37, Joseph, aged 21, is another affected brother. The left iris is brown, the right being brown with a blue sector. The head hair is normal except for scattered patches of white hairs. The eyelids and brows are anomalous (dimensions: 43-65-88).

III-38, a brother, Gerhard, aged 20, has the anomaly of the eyelids (interocular dimensions: 50-63-88) with narrow palpebral fissures (21.5 mm. O.U.). The irides are blue. The nose

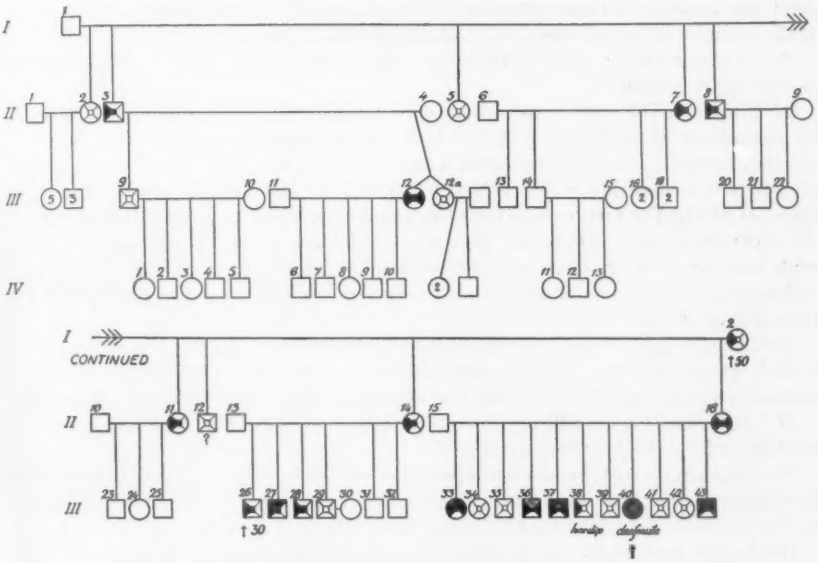


FIG. 17. Pedigree 10, Family Kr-Gi. (For explanation of symbols see p. 201)

root is high and the nose deviates to the right side. I forgot to note the eyebrows. He has also a *bilateral harelip* with *cleft palate.*

III-39, a brother, Aloys, aged 18, is quite normal (interocular dimensions: 33-64-93). The irides are dark olive-brown.

III-41, a brother, Frans, aged 16, is normal with greenish irides. Interocular dimensions: 31-63-87.

III-42, a sister, Johanna, aged 14, is normal with bright blue irides. Interocular dimensions: 30-62-88.

III-43, a brother, Henricus, aged 10 (fig. 16), has *heterochromia iridum;* the right iris is whitish-blue, the left is green with much brown pigment in the lesser circle and at the periphery. The right eye shows no distinct iris frill, and the peripupillary border of the stroma is somewhat hypoplastic. Both irides show a normal pigment border. The pupils are equal and react normally. The fundi are more than average pigmented, perhaps somewhat less pig-

mented in the eye with less iris pigment (O.D.). Vision is normal, with orthophoria, and slight hypermetropia, O.U. The eyebrows are not heavy but are grown together. Interocular dimensions: 43-61-84. There is a large patch of white hair and subjacent spot of depigmented skin on the forehead. There is no sign of dysraphia: standing height 141 cm., span 137.5 cm. The mamillae are equally pigmented and in symmetric positions.

II-15, the father, aged 56, is quite normal (interocular dimensions: 37-66-89), and so is his entire family. He has light blue eyes with some yellow spots.

II-16, the mother, aged 56, shows a white forelock and the typical anomaly of the eyebrows and lids (interocular dimensions: 42-67-89). Both irides are greenish, the right iris having more brown in the temporal half, the left being darker in the nasal half, but there is no definite heterochromia. The nose root is high and broad. The parents of this woman are dead, but according to family information the mother (*I-2*) showed the eye anomaly. *II-16* is the youngest of her 9 children, of which I examined all but one:

II-2, the eldest sister, aged 68, was quite normal (interocular dimensions: 36-63-83), and so were her 8 children.

II-3, male, aged 67, showed the anomaly of the eyebrows, nose root, and eyelids (interocular dimensions: 43-64-87); the irides are blue with peripupillary orange-yellow. He has 3 children, a normal son *III-9* (interocular dimensions: 31-65-87), and a pair of dizygotic twin daughters. The second-born twin (*III-12a*) has fair hair and lacks the syndrome (dimensions: 33-60-83). The first-born (*III-12*) has a dark complexion, and shows the anomaly of the eyebrows and lids (dimensions: 49-62-85), as well as a prominent nose and a *patch of white hair;* her irides are isochromic, darker than the father's, greenish with peripupillary yellow; she has 5 children all normal with respect to the syndrome. The normal twin has three normal children.

II-5, female, aged 65, was normal (interocular dimensions: 33-62-84).

II-7, female, aged 64, showed no anomalies except for a prominent nose and dystopia canthorum (dimensions: 42-65-87). Her husband, 6 children and 3 grandchildren are normal.

II-8, male, aged 62, was afflicted (interocular dimensions: 44-65-89). Iris color: blue, with scattered yellow. His 3 children are normal.

II-11, female, aged 61, has dystopia canthorum (dimensions: 52-68-90) and suffered much from epiphora. The nose root is voluminous. She lacks a white forelock and has blue eyes like her husband and 3 children, all of whom lack dystopia of the inner canthi.

II-12, male, aged 59, lives in Germany, not examined but reported normal.

II-14, female, aged 58, has black hair without white forelock; irides are isochromic yellowish-green with diffuse pigment distribution. But the eyebrow, nasal, and lid deformities are present (dimensions: 50-68-93). She has a normal husband, *II-13*, (dimensions: 32-61-84) and 6 sons, as follows:

III-26, died at age 30 in a railroad accident. Portraits reveal dystopia canthorum and a nose which deviates to the left.

III-27, aged 32, displays *heterochromia iridum* (diffuse olive-brown O.D., bright blue O.S.) in addition to anomalies of the eyebrows, nose, and eyelids (dimensions: 45-68-90). He has no white hair lock, but only scattered white hairs on the head and in the eyebrows. His nose deviates to the right side.

III-28, aged 30, was normal (dimensions: 32-66-88).

III-29, aged 28, was normal, not examined.

III-31, aged 26, was normal, not examined.

III-32, aged 23, was normal, not examined.

Comment: Dominant transmission of dystopia canthi medialis lateroversa is here evident in 3 generations. Whether the affected grandmother displayed other features of the syndrome

is not known, but among her 65 descendants 17 show the eyelid anomaly, 6 with a white forelock and 6 with heterochromia iridum. Congenital deafness occurred only in the probanda, so that were we not aware of other families we would be inclined to assume a fortuitous complication. In this family 2 affected individuals show spots of *hypopigmentation of the skin*, and one case has bilateral cleft lip and palate. A facial asymmetry—deviation of the nose—is present in 4 affected individuals.

Pedigree 11. (Family de Jo, Fig. 19)

This family study developed into such an extensive one that it seems desirable to present the data in a more surveyable tabular form (table 1). There are in reality two probandae, the first being the deafmute with dystopia canthorum (*V-45*) who was called to my attention by Dr. Goedbloed (cf. p. 196). This girl had been an inmate at the institution at Voorburg, but she had now completed her residence there and had returned home. However, the director informed me that he was almost certain that another former inmate was a second cousin of hers. This indeed proved to be another deafmute woman (*V-10*) who was found to possess the syndrome fully developed!

I took the latter case as my starting point and personally saw the majority of the living persons shown in fig. 19. In addition, I examined countless portraits of those who had died, and because many of the living were interested in my research I obtained much reliable information.

V-45. (*Probanda*, Sija v.R., Fig. 18). This 20 year-old deafmute girl has dark hair with a small patch of white hairs in the midline of the forehead which she tries to dye or pull out. She has rather heavy eyebrows, a little bit grown together, a high nose root and blue thin irides. The afflicted mother (*IV-46*) shows heterochromia iridum; the right iris being blue, the left diffuse light brown. Two sibs and the father (*IV-45*) are normal, and so are 3 daughters of his brother and sister.

V-10. (*Probanda*, Maria v.D., Fig. 18), aged 31. This is the only person in the kindred who exhibits the whole syndrome. The anomalies of the nose root, eyebrows and eyelids are very distinct. The right caruncle is normal, the left somewhat enlarged. Originally the head hair was dark brown with a small white forelock, but a large number of grey hairs began to appear several years ago. She is an only child and at the age of 27 had an illegitimate son by a 17-year-old father, whom I could not examine. The little boy, aged 4, has an esophoria which at times becomes a manifest squint. His light blue irides show a very slight heterochromia in respect to deposits of yellowish pigment. The caruncles are perhaps a bit enlarged.

Comment: In this large kindred, comprising 137 persons, we find the dystopia canthi medialis lateroversa transmitted as a dominant abnormality through 6 generations. I was able to actually observe it in 4 generations because *III-2* was still living at 91 years of age. This old woman, who was suffering from lupus faciei with secondary ectropion of the lower lids, was mentally quite normal. She assured me that her mother (*II-2*) had light isochromic eyes with a broad nose root and that the heterochromia iridum in the family was derived from her grandfather (*I-1*) who likewise had the broad distance between the inner eye angles. Altogether there are 40 persons in whom we can record the presence of dystopia canthorum and the broad nose root. In addition to table 1, further notes on this feature in the de Jo family will be found in the discussion on p. 227.

In table 1 there are 16 cases listed in which the eyebrows were definitely grown together, but in reality there must have been many more. I could seldom get precise information on this point in reference to deceased individuals, and portraits are often inconclusive. It is very probable that this symptom is the most frequent one manifested in this family, next to

TABLE 1. FEATURES OF THE SYNDROME OBSERVED IN VARIOUS MEMBERS OF THE FAMILY DE JO (PEDIGREE 11)

PED. NO.	AGE (yrs.)	SEX	DYSTOPIA CANTHI MEDIALIS LATEROVERSA	PROMINENT NOSE	EYEBROWS GROWN TOGETHER	HETEROCHROMIA	IRIS PIGMENTATION O.D. (Right Iris)	IRIS PIGMENTATION O.S. (Left Iris)	WHITE (GREY) FORELOCK	DEAF-MUTISM OR CONG. DEAFNESS	INTEROCULAR DIAMETERS a-b-c (mm.)	OTHER TRAITS
I-1	d.	m.	+	+	?	+	?	?	?	–	?-?-?	?
II-2	d.	f.	+	+	?	–	light	light	?	–	?-?-?	?
•*III-2*	91	f.	+	+	+	–	blue	blue	?	–	49-64-87	ectropion O.D.S., due to lupus
•*III-3*	d.66	m.	+	+	?	–	light	light	?	–	?-?-?	?
III-4												
III-5	d.	healthy										
III-9												
•*III-6*	65	f.	+	+	?	+	grey with fading peripupillar olive	green with peripupilar olive-brown	?	+ deaf at left ear	44-64-87	–
III-7	d.20	f.	+	+	?	?	?	?	?	+	?-?-?	?
•*III-8*	71	m.	+	+	?	–	grey	grey	?	–	45-65-87	–
•*IV-5*	61	m.	+	+	+	–	blue	blue	?	+	44-62-85	–
•*IV-6*	58	m.	+	+	+	–	blue	blue	?	+	44-59-86	–
•*IV-8*	55	f.	+	+	?	–	?	?	+	+	?-?-?	?
•*IV-9*	53	m.	+	+	+	+	grey with naevi	grey with many more naevi	+	+ right ear congen. deaf	42-65-84	–
•*IV-11*	49	f.	–	–	–	+	blue	blue with brown sector at 5 o'clock (iris bicolor)	–	–	33-63-87	–
IV-13	64	f.	+	+	+	–	brown	brown	–	–	?-?-?	premature greying
•*IV-16*	57	m.	–	–	–	–	grey with brownish ring	grey with brownish ring	–	–	28-57-84	–
•*IV-17*	61	f.	+	+	+	+	blue with yellow sector at 1 o'clock	blue with yellow sector at 11 o'clock	+	–	45½-64-85	deaf at later age premature greying
IV-25	52	f.	+	+	?	–	grey	grey	?	–	?-?-?	?
•*IV-28*	46	f.	+	+	?	–	brown	brown	?	–	44-64-88	–
•*IV-37*	34	f.	+	+	+	+	dark olive brown	light blue	+	–	41-58-82	premature greying
IV-39	32	f.	+	+	+	–	brown	brown	–	–	42-63-86	–
IV-41	29	f.	+	+	+	–	grey	grey	?	–	?-?-?	?
•*IV-42*	26	m.	+	+	+	–	greenish grey	greenish grey	–	–	44-64-88	–
•*IV-43*	24	f.	+	+	+	+	blue	greenish brown	–	–	43-62-85	–
•*IV-44*	21	m.	–	–	–	+	blue with brown sector at 1 o'clock	blue	–	–	32-61-84	–
•*IV-46*	45	f.	+	+	+	+	blue	brown	–	–	45-65-87	–
•*IV-48*	43	f.	+	+	?	+	blue	light brown	?	–	44-63-86	–
IV-49	41	m.	+	+	?	–	?	?	?	–	?-?-?	?
IV-54	37	f.	+	+	?	–	?	?	?	–	?-?-?	?
IV-56	36	f.	+	+	?	–	?	?	?	–	?-?-?	?
•*IV-57*	32	m.	+	+	+	–	grey	grey	–	–	44-66-88	asymmetric nose
IV-60	30	f.	+	+	+	–	?	?	?	–	?-?-?	?

TABLE 1.—*Continued*

PED. NO.	AGE (yrs.)	SEX	DYSTOPIA CANTHI MEDIALIS LATEROVERSA	PROMINENT NOSE	EYEBROWS GROWN TOGETHER	HETEROCHROMIA	IRIS PIGMENTATION O.D. (Right Iris)	IRIS PIGMENTATION O.S. (Left Iris)	WHITE (GREY) FORELOCK	DEAF-MUTISM OR CONG. DEAFNESS	INTEROCULAR DIAMETERS *a-b-c* (mm.)	OTHER TRAITS
V-2	32	m.	+	+	?	−	?	?	−	−	?-?-?	?
•*V-10*	31	f.	+	+	+	+	blue	green with olive-brown ring	+	+	44-63-84½	premature greying; lid-fissures 23½
V-26	21	m.	+	+	?	−	light	light	?	−	?-?-?	?
V-27	8	f.	+	+	?	+	brown	blue	?	−	?-?-?	?
•*V-29*	15	m.	+	+	+	−	grey	grey	−	−	40-61-83	−
•*V-30*		f.	+	(+)	?	−	grey	grey	−	−	43-56-78	−
•*V-40*	3	m.	+	(+)	?	−	light brown	light brown	−	−	38-55-77	−
•*V-45*	20	f.	+	+	+	−	blue	blue	+	+	44-62½-85	mental defect
V-46	19	m.	+	+	?	−	?	?	?	−	?-?-?	?
V-47	14	m.	+	+	?	−	?	?	?	−	?-?-?	?
V-50	13	m.	+	+	?	−	?	?	?	−	?-?-?	?
V-55	5	f.	+	?	?	−	?	?	?	−	?-?-?	?
V-58	4	f.	+	?	?	−	?	?	?	−	?-?-?	?
VI-3	5	m.	+	+	+	(+)	blue with yellow at 2 o'clock	blue with nasal yellow	−	−	40-51-72	esophoria, lid-fissures 17

a = inner canthal diameter (mm.), *b* = interpupillary diameter (mm.), *c* = outer canthal diameter (mm.)
• = personally examined individuals. Pedigree numbers refer to fig. 19.
d. = died

dystopia and the prominent nose bridge. In one case (*IV-37*) the hypertrichosis of the eyebrows was accompanied by long eyelashes.

There are 13 positive cases of heterochromia iridum, but in two of them (*IV-11* and *IV-44*) I doubt whether this has any meaning, because these individuals lack other signs of the syndrome and show only a small darker sector in one of their blue irides (so-called *iris bicolor*). So it may be that this happened by mere chance. In the other 11 cases, however, I am convinced that they are part of the syndrome and, as such, significant. The differences in the bilateral picture of the eye colors varied in affected individuals from slight to marked. Other than the presence of a thin blue iris in one eye, I was unable to find any ocular or visual defects in the various members showing heterochromia, with the possible exception of *IV-46* who wore equal corrections but showed on examination a slightly decreased vision in the eye with the darker iris. It may be that a number of persons reported as isochromic would have shown some heterochromia to the skilled observer. Also, a number of irides were blue and hypoplastic, so that a heterochromia could not be manifested. For these reasons, the recorded number of cases must certainly be a minimum estimate.

I found 6 cases in which the syndrome included a white patch of hairs in the midline on the forehead, and in two of these persons there was premature greying. There was also a generalized premature greying in other individuals (*IV-13*, *IV-37*, and *V-10*), so that I got the impression, as in other kindreds, that there may be some connection between the development of these isolated patches in early life and the generalized greying seen in certain individuals.

The pedigree contains 6 cases of congenital deafmutism and 2 cases of congenital unilateral deafness, which seems to be evidence of a most convincing kind that deafness is truly

a part of the syndrome. As far as I could perceive, only one (*V-10*) of these deafmutes exhibits the entire syndrome, but I am not quite sure of this because I was able to examine only 6 of the 8 individuals and two of these (*IV-5* and *IV-6*) could not have demonstrated

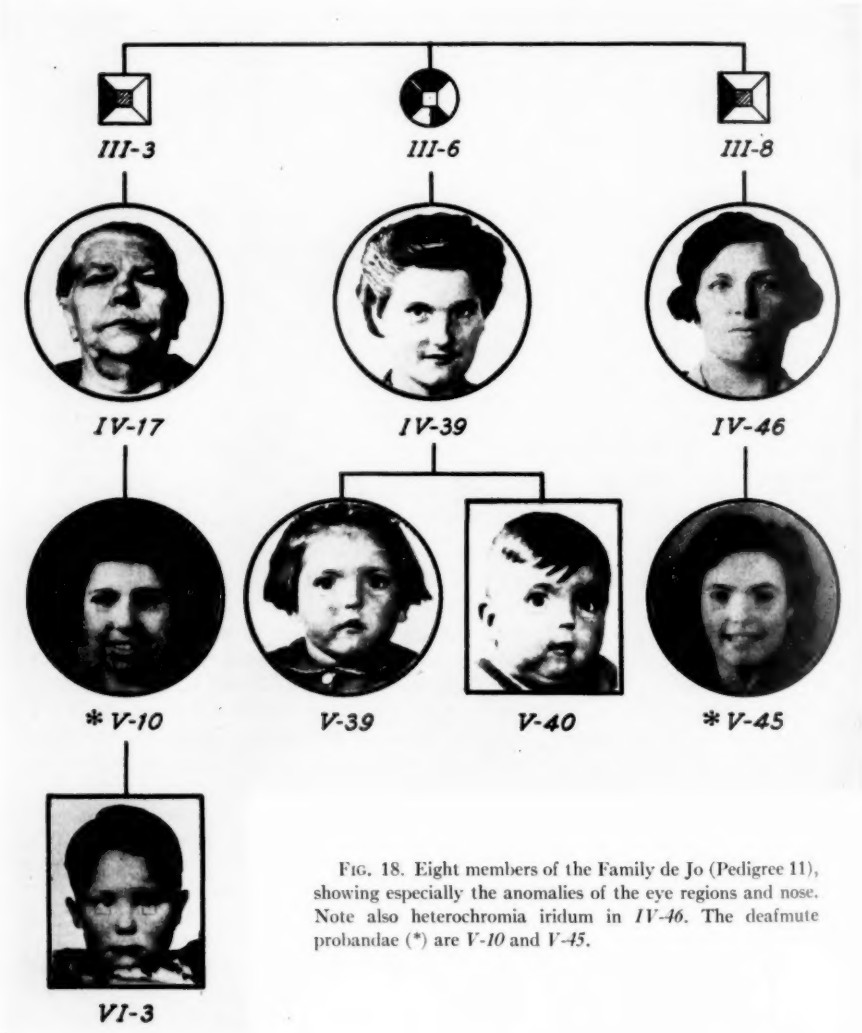


FIG. 18. Eight members of the Family de Jo (Pedigree 11), showing especially the anomalies of the eye regions and nose. Note also heterochromia iridum in *IV-46*. The deafmute probandae (*) are *V-10* and *V-45*.

heterochromia because of their thin blue irides. Concerning one deafmute woman (*III-7*) I could not get adequate information about heterochromia or white forelock. She probably had the eyebrow anomaly, but slight differences in the eye colors or hair shade might have escaped notice or slipped the memory of my informants. The same is true for the two uni-

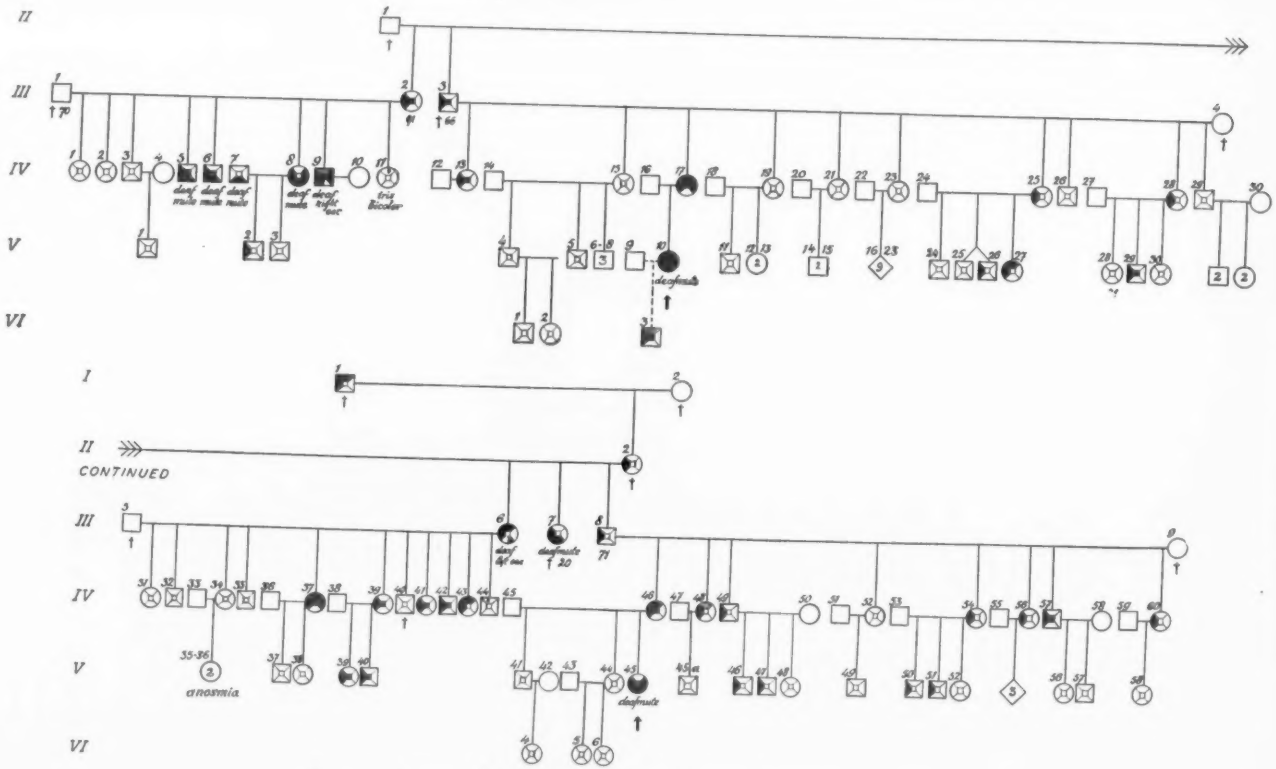


FIG. 19. Pedigree 11, Family de Jo. (For explanation of symbols see p. 201)

lateral cases of deafness, *III-6* and *IV-9;* in these two persons I forgot to note the eyebrows, and *III-6* did not know whether she had once shown a white forelock. Actually *IV-9* comes next to *V-10* in exhibiting nearly all features of the syndrome.

The unilateral cases of deafness are probably best explained as examples of variable expression (penetrance) of the abnormal gene in the two body halves of certain individuals heterozygous for the factor.

This kindred, it will be noted, contains one pair of dizygotic twins (*V-25* and *V-26*) who are discordant for the syndrome.

Pedigree 12. (Family E.V.-de Vr-tenK, Fig. 21)

In Amsterdam the director of the institute told me that long before the last war one of their inmates, a Jewish boy, had shown a peculiar broad distance between the inner eye angles, with small palpebral fissures. This boy (*IV-3*) was the son of two deaf parents. It was quite certain that the mother (*III-5*) had a white forelock, a prominent nose, and an unusual distance between the inner canthi. These same three features, coupled with deafness, were also reported in the mother's brother (*III-3*).

Recently I was able to confirm the above report when, through the courtesy of the family physician, Dr. de Mooy of Amsterdam, information was sent to me concerning the family of another deaf child (*V-5*) who is now a pupil at the institute at Amsterdam. The latter turned out to be a nephew of the aforementioned case, *IV-3*. Through subsequent personal investigations I have been able to complete this pedigree to the extent shown in fig. 21.

V-5. (The *probandus*, Fig. 20). This 3½ year-old congenital deafmute boy has dystopia canthorum (dimensions: 41.5-57-77), with narrow lid fissures (< 20 mm. o.u.) and very long cilia. The irides are brown with a violet-blue periphery. A soft, downy growth of hair is present on the back, extending from the neck to the coccyx. The child's mother relates the following curious history: At birth the right iris was blue and the left iris dark grey; the left soon became brown, but the right did not turn brown until the age of 7 months. Moreover, in infancy there was a conspicuous white lock of hair in the central frontal region, a well-known family trait, but this disappeared in the subsequent hair growth.

V-6, a sister, aged 16 months, appears normal in all respects. Interocular dimensions: 23-43-63. The irides are isochromic, blue with narrow yellowish rings.

V-7, a sister, aged 3 months, is also normal. The irides are grey with a brownish haze.

IV-4, the father, aged 28, is normal. Interocular dimensions: 37-65-91.5.

IV-5, the mother (fig. 20), aged 27, has heavy eyebrows and a white forelock (not visible in the photograph). She is myopic and has dystopia canthorum (dimensions: 42-62-86).

IV-2, the mother's sister, is normal. She married an unaffected first cousin and has four children, all normal.

IV-3, the mother's brother, Samuel E.V., a former inmate at the institute at Amsterdam, was killed by gas poisoning in Germany. He showed the entire syndrome, except for an absence of heterochromia iridum. The irides were described as light brown.

III-4, the maternal grandfather, is deaf, but was not deaf at birth and has no known deaf ancestors or collateral relatives; it is therefore probably an acquired form. He shows no other symptoms of the syndrome. Interocular dimensions: 32-62-84.

III-5, the maternal grandmother, aged 60, was born deaf. In youth she showed a white forelock, but at age 18 she commenced greying and became quite white-headed. The irides are thin, flat, and whitish-blue, of the form often seen in individuals having the syndrome. She also displays dystopia canthorum (dimensions: 45-62-84). Both the superior and inferior puncta lacrimalia are prominent and situated in front of the corneae. Lid fissures measured 21 mm. o.u.

III-1 and *III-2* are reportedly normal sibs of *III-5*.

III-3, a brother of *III-5* who died at the age of 58, was also a congenital deafmute, and shared with this affected sister the other anomalies described. He had no children.

II-2 was reported to be normal with respect to the syndrome.

FIG. 20. Probandus (*V-5*) of Pedigree 12 (Family EV-deVr-tenK) and his mother (*IV-5*)

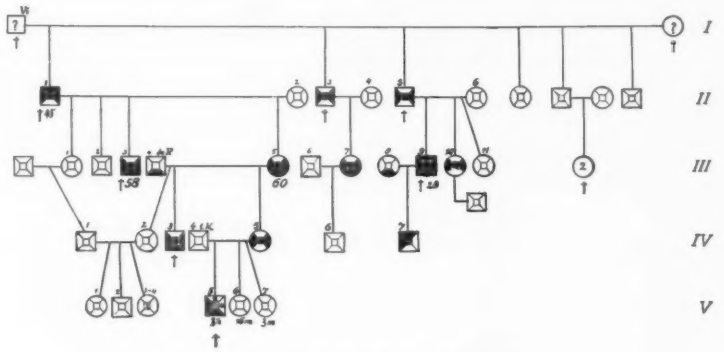


FIG. 21. Pedigree 12, Family EV-deVr-tenK

II-1, D.J.V., great-grandfather of the proband, was seen from a good portrait to have all of the visible signs of the syndrome, including ***heterochromia iridum;*** he lacked deafness, however. As described by *III-5*, the right iris was bright blue, the left brown. It could not be established whether he had inherited the syndrome from his father or his mother, but he had two affected brothers. Concerning them and their descendants the following anamnestic data are available:

II-3, brother of *II-1*, had a broad white forelock and dystopia canthorum. In a marriage

with a normal wife he produced a daughter (*III-7*) having all features of the syndrome except heterochromia, the irides being bright blue. *III-7* is a widow; her deceased husband and her only child, a son (*IV-6*), are reported as normal.

II-5, another brother of *II-1*, showing the same features as *II-3*, produced 3 children by an unaffected wife: *III-9*, a son who died at age 28, had the complete syndrome, with a high asymmetric nose and mixed eye colors (one brown, one blue); with a wife (*III-8*) whose deafness was of a non-genetic form he produced a son (*IV-7*) with one brown and one blue eye, dystopia canthorum and a high nose root, but no white hair lock. *III-10*, the second child of *II-5*, is living at age 66 and shows a mild form of dystopia and hyperplasia radicis nasi; she originally had a white hair lock and later premature greying. *III-11*, the youngest of *II-5*'s children, is normal. There are also three other sibs of *II-5* who are said to lack all symptoms of the syndrome.

Comment: This kindred contains 6 deafmutes in 3 generations, the defect occurring once in mother and son, and twice in sib pairs. White hairlock occurs in 11 cases of the syndrome and heterochromia in 4 cases, counting the unusual case (probandus) in whom both anomalies were described as having been transitory traits in infancy. I am inclined to give credence to this story, and can cite at least one similar report of a disappearing white forelock described by Cotterman and Falls (1949) in a child having multiple unilateral deformities.

Pedigree 13. (Family Schr, Fig. 22)

II-1. (*Probanda*, Dymphna S., Fig. 22). This 9 year-old deafmute girl was found in my examinations at St. Michielsgestel. The palpebral fissures are small, 21 mm. o.d., 20 mm. o.s. The left, rather *microphthalmic*, eye showed a convergent squint, so the interpupillary diameter was not measured (it was probably about 55 mm.); the inner canthal diameter was 37.5 mm., the outer canthal diameter 77 mm. The right inferior lacrimal point is opposite the medial limbus; the left is naturally in front of the cornea. There is a marked *heterochromia*, the right eye being greenish yellow with a blue periphery, the left eye olive-brown. I found two rather small round areas of *skin depigmentation*, one on the front of the right chest and one above the left hip. The head hair is very fair, so that white hairs if present could not be seen.

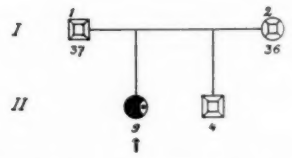


Fig. 22. Pedigree 13, Family Schr, and 10 year-old deaf probanda with heterochromia, dystopia canthorum, and microphthalmic left eye and convergent squint.

II-2, a brother, aged 4, has normal eyes and lids (dimensions: 26-46-71). The irides are blue with some admixture of yellow.

I-1, the father, aged 37, has blue irides. The nose has a high but narrow bridge. There is a normal eyelid configuration (dimensions: 31-58-83).

I-2, the mother, aged 36, has darker irides of an olive-brown or greenish hue, and she has dark hair. The eye region is normal (dimensions: 32-62-84). She had not suffered from rubeola during her pregnancies.

The parents (*I-1* and *I-2*) know of no blood relationship between themselves, nor are there any cases of deafmutism or other congenital anomalies in either family.

Comment: This case probably represents another new mutation. It is uncertain whether the small depigmented skin spots have any significance since a white hair lock could not be established.

Cases of the syndrome not examined by myself

My conversations with the directors of the five institutions for the deaf and with the various families aroused some interest and in this way I learned about a number of additional cases that I was unable to investigate. But it is interesting that the syndrome is one which is not difficult to recognize, even for laymen, and cases of it are apt to make a vivid and long-lasting impression. An example of this was seen in the family de Jo (pedigree 11) where both probandae well called to memory and correctly identified with the syndrome by the director and an oculist after I described the nature of the eyelid anomaly and other features. I am therefore convinced that the following reported instances are essentially correct and may serve to confirm my own observations.

In Groningen I was told that they could well recall a *heterochromic* deafmute, Johan W., whose one eye was brown and the other blue. Whether there had been a dystopia canthorum remained unsolved, but of course this does not mean that the latter symptom did not coexist in this case.

In Rotterdam a former director of the institute remembered the case of a Jewish physician's deafmute son, who had been an inmate there from 1905 to 1908. This boy had always attracted his attention because of the presence of a white lock in the midst of dark black hair and because one eye was brown and the other blue. Our attempt to locate this individual was of no avail and it seems likely that his family may have been exterminated during the German occupation.

The deafmute father (*II-11*) in Pedigree 8 (family Ko-Sp) told me that he knew two deafmute brothers (Q.) in Leiden, one of whom showed an *iris bicolor* like *II-11* himself.

Pedigree 14. (Family E.K., Fig. 23)

In this family my information is limited to the fact that two deafmute first cousins once-removed were both known to display a broad nose root and the typical anomaly of the eye region. Whether other members of this kindred showed partial symptoms or other features of the syndrome is unknown.

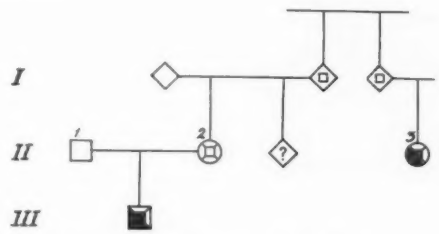


Fig. 23. Pedigree 14, Family E. K.

Peculiar observations of ocular abnormalities in deafmutes, perhaps related to the syndrome

In my examinations conducted at the five institutes for the deaf I observed a number of combinations of eye defects and deafmutism which should, I think, be recorded, as some of them may be felt to offer problems of differential diagnosis with respect to the newly defined syndrome.

The two striking ocular peculiarities found by me in the new syndrome are heterochromia iridum and lateral dislocation of the inner canthi. In the former we are dealing with an underdevelopment of the iris stroma in a bright blue iris or in an iris sector of this color. I have already drawn attention to the fact that persons who are genetically destined to have both eyes blue or grey, or, at any rate nearly devoid of stromal pigment, cannot exhibit heterochromia on any genetic basis whatsoever. However, the blue or grey-blue found in the heterochromic eye is not of the common type but is a special whitish-grey or whitish-blue, produced by a normally developed anterior border layer and a very hypoplastic stroma and vessel layer between the border and pigment layers, giving the iris a very flat and thin appearance (see p. 219).

Since I found familial cases with heterochromia but without dystopia canthorum, it seemed worthwhile to record those deafmute cases having a hypoplasia of one or both irides, with or without other anomalies. Such cases were observed.

The following cases displayed the condition with *isochromia:*

Case 1. (St. Michielsgestel). Theo S., male, aged 10, has thin dystrophic irides of the above-mentioned type, without the eyelid anomaly.

Case 2. (St. Michielsgestel). Bea Br., female, aged 9, shows very thin diaphanic irides and normal eyelids.

Case 3. (Groningen). Nico van D., male, aged 11, has congenital deafness, hypoplastic irides, coloboma iridis o.d., and marked hypermetropia and astigmatism o.u. Vision with correction, 6/8 o.d.; 6/6 o.s. The non-consanguineous parents and an older brother are normal.

Case 4. (Amsterdam). Maria B., female, aged 12, is a congenital deafmute with defects of the iris, consisting of a very hypoplastic stroma o.u., which was diaphanic over most of its extent to transscleral illumination, and ectopia pupillae o.s., the pupil being ectopic in the upward-outward direction. One is inclined to ask whether the left eye exhibits one of the well-known forms of progressive iris atrophy. That such cases need not belong to the syndrome described in this paper is clear from other observations which I made. For example, at Groningen I saw a hearing mute (Johanna A., aged 11) with an almost total aplasia of the stroma of both irides and a slight ectopia of the left pupil nasally and upward. On the other hand, it would be most desirable to clear up whatever connections may exist between deafmutism and hearing mutism. In St. Michielsgestel I saw a boy who suffered from deafmutism and myxoedema. Two of his brothers were mentally defective deafmutes and one sister was a hearing mute. In Rotterdam there are a sister and brother, both hearing mutes, who have two normal sibs and parents who are related as first cousins. Miss Kamerbeek (1949) reports in her material on deafness caused by rubella three cases of "mental deafness" (hearing mutism or "slow hearing") and she tells us (p. 40) that the inner ear in mentally deaf patients is not always untouched.

The following examples of *heterochromia* without the eyelid anomaly came under my observation:

Case 5. (St. Michielsgestel). Bep N., female, aged 11, has congenital deafness, with heterochromia iridum (light brown o.d., light blue o.s.) but no other anomalies of the eyes or symptoms of the syndrome.

CASE 6. (St. Michielsgestel). Marlientje L., female, aged 5, has congenital deafness with no other anomalies except a partial heterochromia iridum. The right iris is brown, the left blue except for sectors of dark brown from 4 to 6 o'clock and light brown from 8 to 11 o'clock. This child is a curly-headed mulatto, the father being Dutch and the mother a native of Curaçao.

CASE 7. (St. Michielsgestel). Ida S., female, aged 53, a born deafmute, showed heterochromia iridum; the right iris is blue, the left brown. The palpebral fissures show no abnormalities, the lacrimal points are normally situated, and the interocular dimensions are 37-67-87. I could not investigate the relatives of this woman. As for the displacement of the inner eye angles and lacrimal points, one should reckon with the possibility that its expression may be a feeble one in this instance and that abortive forms of the anomaly may exist. I indeed came across such cases, but they were only once combined with iris atrophy and never with heterochromia, so I have omitted them here.

Deafmutism is seldom seen in association with other congenital anomalies. I saw cases of Usher's syndrome (deafmutism with *dystrophia retinae pigmentosa*) and cases with some forms of dysfunction of the extraocular muscles, and with certain skeletal anomalies (Klippel-Feil synostosis of the cervical vertebrae), anomalies of the outer ear, and anomalies of the hands, etc. It would be worthwhile investigating deafmutes systematically for such malformations.

DYSTOPIA CANTHI MEDIALIS LATEROVERSA AS THE MOST FREQUENT ANOMALY

Of the several features of the syndrome, the eyelid anomaly, *dystopia canthorum*, deserves first consideration for a number of reasons. Although congenital deafness is the most serious complication occurring in the syndrome, and being responsible for the institutionalization of cases thus serves as the most convenient basis for selection of probands, the auditory defect is actually one of the least frequently expressed components of the syndrome. Dystopia canthorum, on the other hand, appears to be the most regularly expressed feature seen among the relatives of the probands. Furthermore, it lends itself to objective measurement and thus provides an opportunity to show that the syndrome as a whole is a distinct segregating complex, as will be brought out in a statistical note, published as an addendum to this paper by Dr. Cotterman.

It is a peculiar thing that in photographs this dystopia often does not seem very pronounced, but in reality one will seldom miss on behalf of the diagnosis. Indeed, the defect is usually apparent at first glance, even to laymen. Especially in childhood the anomaly is very striking, and even at this age the outgrowth of the nasalia, producing the broad high nose root, is already apparent. In the family de Jo (ped. 11), for example, the inner canthal diameter varies between 41 and 49 mm. in the affected adults, but it has already reached 40 mm. in a 5 year-old boy (*VI-3*).

The picture may be so striking as to give the illusion that a convergent squint is present. Actually, I encountered only one case (ped. 11, *VI-3*) in which there was a genuine latent strabismus (fig. 18) which became manifest under emotional stress. In young children displaying the dystopia the sclera may be wholly invisible on the medial side of the cornea, even though there is no true

epicanthus. It may happen that the inner canthus closely joins the medial limbus corneae, and in some cases the caruncula lacrimalis may be somewhat enlarged (e.g. ped. 11: *V-10* and *VI-3*, O.U.; *IV-17*, O.S.). Usually, however, the caruncula is of normal size, and all cases show a normal-sized plica semilunaris.

Evidently when the individual with dystopia canthorum grows older the nasal part of the sclera usually becomes a bit exposed, but generally the distance between the inner eye angles remains greater than that between the wings of the nose. On the other hand, the prominence of the nose root in many of the older individuals tends to compensate for the increased inner canthal distance and de-emphasizes the impression of a broad nose root. In general, both the nasal and lid changes are quite symmetrical, and other facial asymmetries are not often in evidence. In a few individuals, however, the dystopia seems to be displayed more markedly on one side, and there may be a deviation of the nose bridge to one side (pedigrees 1, 5, 11, 12). The interpupillary and outer canthal distances are wholly within the normal range of variation, so that in general there seems to be no tendency for hypertelorism to accompany the anomaly, although such may occur incidentally, as in family Na (ped. 2) and perhaps in family Vi (ped. 9).

I agree with van der Hoeve, who has demonstrated two cases (1930, 1934), that *dystopia canthorum* and *hypertelorism* may occasionally occur together. An extreme case of this association, with other anomalies, was shown to me by Prof. Sillevis Smitt, at the neurological clinic at Utrecht. I perceived at once that the hypertelorism was combined with dystopia canthorum, as the lacrimal points were situated opposite the corneae and nearly all of the sclera was concealed on the nasal side. This 2 year-old boy had the following interocular dimensions: 57.5 (!), 73.5 (!), 98, and the lid fissures measured 20.5 mm. The irides were blue. There was a large frontal swelling with a hemangioma of the skin at the level of the nose root, a palatoschisis and median notch of the upper lip, and cryptorchism. X-ray photographs revealed a central hyperostosis in the region of the ethmoid and frontal bones. So, evidently, various anomalies of the skull may be associated with both hypertelorism and dystopia canthorum, as a result of the actions of different genes. As a further example I reproduce here an illustration (fig. 24) of a case of unilateral dystopia canthorum which I previously described in a case of *acrocephalia* (Waardenburg, 1934).

Such occasional coincidences of the two anomalies, however, must not be allowed to seduce us into the position of supposing that they are one and the same. Hypertelorism and dystopia canthorum have quite separate origins and distinct differentiating features (cf. p. 196). Much confusion exists in the literature, and I must confess that well-intentioned colleagues have sent me on many a futile search because of their mistaken diagnoses. So I cannot urge too

strongly this distinction between the two conditions, and I reproduce here, for comparison, two typical illustrations (fig. 25) of hypertelorism from a publication by Halbertsma (1929*b*).

FIG. 24

FIG. 25

FIG. 24. Male patient with acrocephalia, facial asymmetry and unilateral dystopia canthi me lialis lateroversa. After Waardenburg (1934) in *Nederlandsch Tijdschrift voor Geneeskunde*, 78:1700.

FIG. 25. Brother and sister with hypertelorism, an anomaly not to be confused with dystopia canthorum. After Halbertsma (1929) in *Bollettino di Oculista*, 8: 3.

GENETICAL AND STATISTICAL CONSIDERATIONS

Genetics of the syndrome as a whole

I assume the syndrome to be inherited in an autosomal dominant way. In the sibships usable for an analysis of the expected 1:1 segregation (peds. 5, 6, 7, 8, 9, 10, 11 and 12) 83 sibs are normal and 87 affected. As to sex, the dystopia canthorum component was present in 64 males and 52 females, heterochromia iridum in 19 males and 15 females, deafness in 21 males and 13 females, and white hairlock in 12 males and 15 females. Considering the total frequencies of males and females in the sibships, these differences are not significant. It is striking, however, that the general finding that deafmutism is more common among males is again noticed in this material. It seems as if the male is more disposed to reveal deafness.

Both sexes transmit the syndrome to both sexes, and in particular there are numerous instances of father-to-son transmission. So X-chromosomal inheritance is excluded. However, there is a slight suggestion (table 2) that the gene might be located on the homologous segments of the X and Y chromosomes (partial sex-linkage). The deviations suggesting this are somewhat heterogeneous and nonsignificant in the totals, but the problem deserves attention in future studies.

I assume mutation to be responsible for the sporadic cases represented by the probands of pedigrees 1, 2, 3, 4, and 13. If this is the case, then we see that the first bearer of the gene may be a deafmute. We of course do not know in the other pedigrees which individuals were the original recipients of mutations or what features of the syndrome they possessed. However, there seems to be no objection to the supposition that the mutation in its first bearer may manifest

TABLE 2. CLASSIFICATION OF CHILDREN OF AFFECTED PARENTS AND TEST FOR PARTIAL SEX-LINKAGE.

PEDIGREE NO.	CHILDREN HAVING AFFECTED FATHERS AND AFFECTED								CHILDREN HAVING AFFECTED MOTHERS AND AFFECTED							
	GRANDFATHERS				GRANDMOTHERS				GRANDFATHERS				GRANDMOTHERS			
	□	■	○	●	□	■	○	●	□	■	○	●	□	■	○	●
5	2	2	5	2	3	1	2	1	1	6	1	3	0	1	1	1
6	—	—	—	—	—	—	—	—	2	1	0	0	—	—	—	—
9	—	—	—	—	0	1	1	0	—	—	—	—	—	—	—	—
10	—	—	—	—	3	0	2	1	4	0	1	0	11	7	5	2
11	1	2	2	0	2	2	5	9	4	6	5	6	7	7	6	6
12	0	1	0	0	—	—	—	—	1	1	1	1	0	1	2	0
Total	3	5	7	2	8	4	10	11	12	14	8	10	19	18	14	10

* indicates cross-over classes (x) on hypothesis of partial sex-linkage.
For all children of affected males, $x = 19/50$, giving $\chi^2 = 2.88$, and $P = 0.09$.
Counting affected children of males, $x = 6/22$, giving $\chi^2 = 4.55$, and $P = 0.03$.
Counting normal children of males, $x = 13/28$, giving $\chi^2 = 0.14$, and $P = 0.71$.

itself in any feature of the syndrome or any combination of these features; if so, then each of the component anomalies might be absent in the sporadic or mutational case, including even dystopia canthorum which has the highest penetrance of the several features. Nevertheless the future must decide whether these isolated cases are really heterozygotes for the same dominant gene, and whether the probands of pedigrees 4 and 8 and similar individuals which I observed really belong to the same syndrome, even though dystopia canthorum is absent.

I must admit that one or more additional genes might sometimes play a role, and these might be either genes at different loci or polyalleles at the same locus. The latter could possibly serve to explain Klein's serious case, which is the only one revealing skeletal and muscular defects and such a marked degree of development of the other anomalies. It is a peculiar fact that this girl was the first in her family to exhibit these anomalies which occur in her in such outspoken form. If, instead of assuming another, though perhaps allelic mutation, we assume that Klein's syndrome is actually due to the same mutation responsible for the more common cases observed by me, then one might sug-

gest that Klein's patient is a homozygote taking its origin in some unusual way such as non-disjunction of a special autosome or part of it, or that the case is, as Klein himself supposes, an instance of translocation or some other kind of irregularity in the distribution of chromosomes. Another possibility would be the loss of a part of a chromosome (deletion). There is no reason to assume recessive inheritance in this case, since the normal parents are not known to be related. However, there is also nothing to contradict this possibility, and one must recall that human genetics knows many examples of clinically similar entities which are more serious in their effects when the gene behaves as a recessive, rather than as a dominant.

Degrees of penetrance of the various component anomalies

To get an idea of the degree of penetrance of each anomaly occurring in the syndrome I have summarized the family data for my own series of probands in table 3. As will be seen in a later section, each of the anomalies comprising the syndrome has been previously identified as a single hereditary trait, and there are a few publications dealing with combinations of certain of these characteristics. In the latter cases, however, one cannot be sure that the authors systematically observed or recorded each trait for all relatives. It seems best, therefore, to restrict the analysis to my own material.

Table 3 shows, for each proband, the particular combination of anomalies observed in the proband, the total number of relatives classified as possessing the syndrome, and the frequencies of these relatives possessing each of the 6 component anomalies. In estimating the degree of penetrance for each feature, the probands must clearly be excluded from the column for deafness, as all were selected for this anomaly. Furthermore, in order to qualify as examples of the syndrome each had to possess at least one of the other anomalies, and in fact most of them showed several features. So I have excluded the probands altogether and have enumerated only the relatives of these probands in the figures given in the body of the table. There is, however, one important exception: in cases where there are two probands (peds. 5, 6, 11) the entire kindred is scored twice, once for each proband; since the proband is omitted each time, this amounts to scoring each proband once and all other affected individuals twice. In the case of pedigree 6, containing probandae who are MZ twins, it seems appropriate for the present purpose to consider the twins as two individuals, and to score them as in the other two kindreds having two probands.

As was seen in the previous section dealing with the descriptions of the 14 kindreds, the eyelid anomaly (dystopia canthorum) serves as an almost infallible indicator of the presence of the syndrome, this feature being almost invariably present when one or more of the other anomalies are present. In other words, the penetrance of this component seems to be almost complete. Had

TABLE 3. FEATURES OF THE SYNDROME EXHIBITED BY THE PROBANDS, AND FREQUENCIES OF EACH ANOMALY AMONG RELATIVES POSSESSING THE SYNDROME

The presence (+) or absence (−) of each anomaly is shown for the proband, followed by the number (in parentheses) of affected relatives (proband excluded) showing the anomaly. Pedigrees 5, 6 and 11 each contain 2 probandi, both of whom are then counted with double scoring of the other affected relatives. The totals provide minimal estimates of the *degrees of penetrance* of the six anomalies comprising the syndrome.

FED. NO. (Family)	TOTAL NUMBER OF AFFECTED RELATIVES SCORED	DYSTOPIA CANTHI MEDIALIS LATEROVERSA	PROMINENTIA RADICIS NASI	HYPERPLASIA SUPERCILII MEDIALIS	HETEROCHROMIA IRIDUM (TOTALIS SIVE PARTIALIS)	SURDITAS CONGENITA (SURDIMUTITAS)	ALBINISMUS CIRCUMSCRIPTUS PILORUM
1. RO	0	+ (0)	+ (0)	+ (0)	− (0)	+ (0)	? (0)
2. NA	0	+ + (0)	+ + (0)	± (0)	+ + (0)	+ + (0)	? (0)
3. JA	0	+ + (0)	+ + (0)	+ + (0)	+ + (0)	+ + (0)	− (0)
4. BO	0	− (0)	+ + (0)	+ + (0)	+ + (0)	+ + (0)	+ (0)
5. DRU	44	+, + + (44)	+, + + (20)	+, + + (16)	+, + + (12)	+, + + (6)	−, − (0)
6. R. S.-S. S.	6	+, + + (6)	+, + + (6)	+, + + (2)	−, − (0)	+, + + (4)	−, − (2)
7. SCHU	2	+ + (2)	+ + (2)	+ + (2)	− − (0)	+ + (0)	+ (0)
8. KO-SP	2	− (0)	− (0)	− (0)	+ + (2)	+ + (2)	− (0)
9. VI	2	+ + (2)	+ + (1)	+ + (1)	− (0)	+ + (0)	+ + (0)
10. KR-GI	16	+ + (16)	+ + (14)	+ + (14)	+ + (5)	+ + (0)	+ (5)
11. DE JO	78	+, + + (78)	+, + + (72)	+, + + (28)	+, − (19)	+, + + (14)	+, + (10)
12. E. V.-DE VR-TENK	10	+ + (10)	+ + (10)	+ + (10)	+ + (3)	+ + (5)	+ (10)
13. SCHR	0	+ + (0)	+ + (0)	+ + (0)	+ + (0)	+ + (0)	− (0)
14. E. K.	1	+ + (1)	+ + (1)	+ + (0)	? (0)	+ + (1)	? (0)
Totals	161	(159)	(126)	(73)	(41)	(32)	(27)
Estimated Penetrance (per cent)		99	78	45	25	20	17

this not been the case, a more complicated analysis of the data would have been necessary, for we would then have to reckon with the probability of certain heterozygous individuals lacking all expressions of the syndrome. A few such cases may indeed occur, but a failure to consider them seems unimportant in arriving at the present approximate estimates.

Pedigrees 1, 2, 3, 4, and 13 are included in the table for the sake of completeness. Since these five probands were found to have no affected relatives, yet as probands exhibited several features of the syndrome, they are regarded as being very likely new mutations. As such, these families afford no information about the penetrances, and are so treated by the procedure of counting only relatives.

I wish now to stress the fact that the estimated penetrances for some of the anomalies are almost certainly underestimates or miminal values. In the case of the hyperplasia of the eyebrows I have already mentioned that I was not aware of this feature in the early phases of the study, and in a few cases I neglected to record the status of the eyebrows and the nose root. As for the white forelock, the reader will have seen from the family descriptions that we are seldom dealing in this syndrome with the broad and conspicuous "white blaze" which is described in many pedigrees of so-called circumscript albinism. Often we see only a small bundle of white hairs in the midline of the hair margin. A few individuals make an effort to obliterate the feature, some bald men may have forgotten they once possessed the trait, and we must even reckon with the possibility that in some individuals the defect may have existed only temporarily in infancy or youth. Consequently, since a considerable number of the individuals included in table 3 are known from photographs or family reports only, this feature almost certainly has a penetrance in excess of 17 per cent.

Heterochromia iridum also exists in very minor form in some individuals, so that it would not be recognized even by the person affected, let alone reported by his relatives. When one iris is blue and the other has only a trifling yellowish pupillary ring, special training is needed in order to see the difference and make the diagnosis of heterochromia. Moreover, 'heterochromia iridum' as a designation for the anomaly is probably incomplete for this reason: What is the meaning of isochromic blue eyes in persons having the syndrome? Do they lack heterochromia because having inherited other genetic factors causing them to have blue eyes the gene for the syndrome is unable to be expressed, or is the hypoplasia in such cases a complete and bilateral one? I think both of these events occur. I saw isochromic blue irides in several cases of the syndrome where I did not hesitate to diagnose a bilateral hypotrophy with hypochromia. There were other affected persons with blue eyes differing in no observable way from normal blue irides. But lacking a precise criterion for

this separation, I have classed all individuals lacking a true heterochromia as negative. So again, for various reasons, the figure of 25 per cent penetrance doubtless underestimates the gene's activity.

Coming finally to deafness, I think that the figure of 20 per cent penetrance is probably more accurate than the others, since congenital deafness is much more apt to be reliably reported in unexamined individuals. This is not to say, however, that the gene is wholly without effect in the remaining 80 per cent of carriers of the syndrome, and it would seem worthwhile looking for minor defects, for example by audiometric studies of affected families.

If the question should be raised as to whether, having perhaps accidentally observed this syndrome first in deafmutes and having indeed found other cases in the institutes for the deaf, the syndrome though inherited might have no true connection with deafness, then my finding that about 20 per cent of all relatives *having the syndrome* are congenitally deaf seems to dispel all doubt in this direction. It is true that deafmutes sometimes intermarry, but whenever I found deafmutism in descendants it was always in individuals having other features of the syndrome, and similarly with other relatives of the probands. This we would certainly not expect in families taken at random, if deafness were not a part of the syndrome. Furthermore, even without recourse to the family data, the fact that about 1.4 per cent of deafmutes were found to have the syndrome including dystopia canthorum seems to be sufficient evidence in itself, since the syndrome (excluding deafness) can certainly not have such a high frequency in the general population.

It is evident that some kindreds show a higher penetrance for certain features of the syndrome than do others. For example, not one of the affected members of the rather large Dru kindred (ped. 5) revealed a white hairlock, whereas this was present with high frequency in pedigree 12. The same is true for deafness; the rather large pedigree 10 contains only one case (the proband) while pedigree 12 contains 6 cases. On the other hand, heterochromia iridum is rather abundant in pedigrees 5, 10 and 11, but rare in pedigree 12. Our general insight with respect to constitutional or genetical factors is at present insufficient to explain these differences. The total genetic constitution of various family members being often very different, it seems more likely that we may be dealing with the effects of linked modifying genes.

Frequency of the syndrome among deafmutes and in the general population

Some interesting calculations may be made relating to the frequency of the new syndrome. Among the personally examined institutionalized deafmutes I found the proportion of cases of the syndrome to be

$$\frac{12}{840} = 1.43 \text{ per cent.}$$

The denominator in this fraction (840) is an estimate of the number of congenitally deaf persons among the total number of 1050 inmates examined at the five institutes, based upon data supplied by Mr. C. Timmer, director of the institute at Voorburg.[3] The numerator (12) consists of all cases found in this survey and regarded as examples of the new syndrome, including the probands of pedigrees 4 and 8, which are familial cases lacking, however, dystopia canthorum.[4] (If I also accept 3 solitary cases found in the same survey, possessing heterochromia but without dystopia canthorum, this raises the frequency to 15/840 or 1.78 per cent.)

It seems reasonable to suppose that the same frequency (1.43 or 1.78 per cent) would obtain among non-institutionalized deafmutes, and that we may therefore take this figure as an estimate of the fraction of all deafmutes in the Netherlands who owe their deafness to the irregularly expressed dominant form occurring as a part of the new syndrome.

For the total incidence of deafmutism in our country the most recent information that I could procure[5] would place this proportion at 33 per 100,000 population, or 1 per 3,030. Multiplying this by the observed proportion of cases of the syndrome among deafmutes gives

$$\frac{1}{3{,}030} \times \frac{12}{840} = 0.00047 \text{ per cent},$$

or about 1 per 212,121 for the estimated population incidence of cases of the *syndrome including deafness.*

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[3] Timmer (1948) has published data, covering the years 1934–1940, which reveal that about 20 per cent of institutionalized pupils are not deafmutes, but "hard of hearing" or hearing mutes. The number 840 was therefore taken as 80% of 1050, the total number of inmates seen at the 5 institutes.

[4] The 12 cases include probands for pedigrees 2, 3, 4, 5, 7, 8, 9, 10, 11, 12 and 13, counting 2 probands in pedigree 5, both of whom were located at the institute. The probands of pedigrees 1 and 6 were not discovered through this survey.

[5] De Wilde (1913) took census data for 1909 and estimated the incidence of deafmutism to be 39.34 per 100,000. Van Dishoeck (1949) estimated 40 per 100,000 in that year. Cases of deafmutism were enumerated in 3 official censuses up to 1920, but not since that date:

	Male	*Female*		*Deafmutism, per 100,000 population*	
Year	*deafmutes*	*deafmutes*	*Total*	*Male*	*Female*
1889	1087	890	1977	48.8	39.0
1909	1228	1077	2305	42.4	36.4
1920	2346	2011	4357	68.8	58.2

Such data are however subject to the criticism that they include the uncritical judgments of laymen. The marked increase in 1920 seems unlikely. The excess of male cases is always apparent, as is found in other countries.

Recent information furnished me by the Central Bureau of Statistics at the Hague shows that the average duration of life of deafmutes scarcely differs from the average for the whole population. Utilizing Timmer's data on institutionalized cases, this Bureau estimates the following numbers of deafmutes for the entire country: 3000 in 1946, 3100 in 1947, 3100 in 1948, 3200 in 1949, and 3300 in 1950. For the period of my survey I have therefore adopted the figure of 33 per 100,000.

The incidence of the syndrome in its entirety, i.e. *with or without deafness*, should of course be much larger. Multiplying, therefore, by the reciprocal of the estimated penetrance of the deafness component (cf. p. 232) gives

$$\frac{1}{212{,}121} \times \frac{100}{20} = 0.00236 \text{ per cent},$$

or about 1 per 42,000 for the frequency of the syndrome in the population. For a rare dominant autosomal gene, the frequency of heterozygotes will be very nearly twice the *frequency of the abnormal gene*, which may therefore be taken as about 1 per 84,000 genes.

In a population of 10 millions, we see that about 47 cases of the syndrome including deafness would be expected to be now living in the Netherlands. In my family studies I found actually 29 such cases now living, or about 62 per cent of the expected total. Five of the cases in my pedigrees (pedigrees 11, 12, and 14) are deceased. Furthermore, in the entire population we would be led to expect 236 cases of the syndrome, and 91 were brought to light in my family studies, or 39 per cent of this number. No doubt many of the assumed remaining or undiscovered cases, both with and without deafness, must be members of the 14 kindreds already on record, for in all instances my family inquiries were arbitrarily limited in scope. The fact that my investigations uncovered a larger proportion of the total number of Dutch cases including deafness, as judged from the above calculations, is not surprising. All of the families were selected through deafmute probands, and these probands, together with their deaf relatives showing the syndrome, are enumerated in the totals, 29 and 91, cited above. These same probands, however, were naturally omitted in estimating the degree of penetrance of the auditory defect; if the same deductions were made here as in table 3, the results would necessarily be exactly in the ratio 20:80 except for the further exclusion here of a few affected relatives who are deceased or live outside of the Netherlands.

Obviously the number of Dutch kindreds having the syndrome which have not yet come to my attention must be relatively small. Moreover, considering that van der Hoeve, who first described dystopia canthorum with blepharophimosis, collected in 35 years only a small number of *uncomplicated* cases, and that any one of the 150 oculists in our country may work several years without seeing a single case, I really wonder whether cases exist of a *simple* dystopia canthorum other than those which are carriers of the syndrome.

It may be noted that five of the kindreds (pedigrees 1, 2, 3, 4 and 13) contain what appear to be solitary cases of the syndrome, suggesting the occurrence of new mutations. Assuming these to be heterozygotes for the same dominant gene which is evidenced in the pedigrees of 11 other probands (taking all probands, including those discovered outside of the institutes, and counting the twins in pedigree 6 as a single individual in this case) the ob-

served proportion of "new" or "mutational" cases is 5/16. Applying then the so-called "direct method" of estimating mutation rates, we see that the estimated gene frequency of 1 per 84,000 suggests a *mutation rate* of about 1 per 270,000 gametes. This is considerably less than the mutation estimates which have been suggested for a number of other pathological human genes. The above calculation involves, of course, one assumption on which at present no data are available: we assume that new or mutational cases are no more or no less likely to exhibit deafness as a part of the syndrome than are "old" or inherited cases. A series of pedigrees starting with probands lacking deafness would be needed to check this assumption. But, unless it should be that mutational cases are much *less* likely to involve deafness, it seems difficult to see how our present data on the Netherlands could be reconciled with a much higher mutation incidence.

Having expressed the frequency of the syndrome among deafmutes in general and among the total population, it might seem desirable to also state the frequency among all cases of endogenous or hereditary deafness. This requires knowing the frequency of hereditary deafmutism among the total population of deafmutes. Unfortunately there is no easy way to obtain reliable or even very meaningful estimates of this fraction. From reports of congenital deafness in which the occurrence or non-occurrence of familial cases or parental consanguinity was mentioned, I found a frequency of 25–33 per cent in our country. But I suspect this is much too low a figure, and I doubt further whether estimates that have been quoted for other countries will enable those studying the new syndrome to compare our countries in this way. Even if the fraction of hereditary cases were accurately known in various countries, we would have little information regarding the frequency of the gene for the syndrome relative to other genes causing deafness, unless we also knew the proportions of dominant and recessive genes among these other types, the different frequencies of inbreeding in each country, etc. It is important, of course, to realize that the frequency of the syndrome among deafmutes might be quite different in two different countries even though the gene frequency is the same for both, and that this might be due to differences in hygienic conditions responsible for various forms of exogenous deafness as well as varying frequencies for other forms of hereditary deafness.

INHERITANCE OF THE SEPARATE ANOMALIES AND THEIR COMBINATIONS IN MAN AND OTHER MAMMALS

Curiously enough—yet not without parallel among the many genetic syndromes known in man—each of the component anomalies of the new syndrome has been recognized as a separate hereditary trait. In this section, I shall briefly review the literature for each feature of the syndrome, calling attention where possible to those peculiarities of the particular anomalies occurring in

the syndrome which may possibly offer a means of distinguishing them from separately inherited anomalies which they may resemble. The literature bearing on the inheritance of similar complexes in other mammalian species will also be summarized.

Dystopia canthi medialis et punctorum lacrimalium lateroversa

Consulting the literature on this anomaly, I found only the above-mentioned pair of twins reported by van der Hoeve (1916), 2- and 3-generation pedigrees described by Halbertsma (1929*a*), a 4-generation pedigree by Leonardi (1931), a 4-generation pedigree by Lisch (1934), a 3-generation pedigree with concordant twins by John (1934), a 3-generation pedigree by Morganti and Musini (1948), and solitary cases reported by van der Hoeve (1929), Braendstrup (1941), Bellecci (1946), and Malatesta (1948).

It struck me that in the families reported by Leonardi and by John mention is made of *heterochromia iridum*. Leonardi records a pronounced heterochromia in a boy having the typical eyelid anomaly (fig. 26); the mother of this boy had both anomalies in milder form. John found total heterochromia in a girl, and a partial sector-like heterochromia in the right eye of her younger sister (fig. 27, *left*); a woman belonging to an earlier generation had the eyelid defect and very light blue eyes (fig. 27, *right*). It is also interesting that in the pedigree of Morganti and Musini an affected woman and a non-affected man in the first generation were said to be *deafmutes*.

FIG. 26

FIG. 27

FIG. 26. Four year-old male with heterochromia iridum and dystopia canthi medialis lateroversa, the probandus in Leonardi's 4-generation pedigree of the latter anomaly. After Leonardi (1931) in *Bollettino di Oculista*, 10: 165.

FIG. 27. Nine year-old girl with hypopigmented nasal upper quadrant of the right iris and an aunt having bright blue irides, two members of John's 3-generation pedigree of dystopia canthorum and blepharophimosis. After John (1934) in *Von Graefes Archiv für Ophthalmologie*, 133: 60.

I am convinced that these pedigrees belong to my syndrome and hope that further genetic studies of the eyelid anomaly may be published in order to

decide whether it really exists as a separate genetic trait, or whether it is always combined with other anomalies, such as ptosis and other muscular defects of the eye in the hereditary cases of van der Hoeve (1928, 1929), Waardenburg (1930) and Tirelli (1932), and in the solitary case of van der Hoeve (1939), or with acrocephalia, as seen unilaterally in two male cousins by Waardenburg (1934), or with the several features of the new syndrome herein described.[6]

It may be noted in passing that almost all of the previously published accounts of this eyelid anomaly have been accompanied by pedigrees of varying sizes showing dominant inheritance. This fact seems of interest in connection with two facts brought out in the present study, namely that the defect which occurs in the present syndrome shows a high degree of distinct expression, and that its penetrance, among the various components of the syndrome, seems to be highest of all.

Hyperplasia supercilii medialis et radicis nasi

To my knowledge only one pedigree of hypertrichosis of the eyebrows has been published (Orel, 1931; 4 generations). However, we know from twin studies that MZ twins are almost always concordant for this trait, whereas DZ twins are commonly discordant (von Verschuer, 1931; Diehl & von Verschuer, 1933; Jancke, 1947). I personally know of families in which a heavy eyebrow is inherited as a dominant characteristic. In the majority of such cases the eyebrows are confluent, being joined by rows of hairs of normal color. In nearly all cases there is, in adults, an associated high nose root or bridge. The distinguishing feature in the present syndrome is this: here it is chiefly the medial portion—the so-called head—of the eyebrow that is hyperplastic, and especially when they are grown together it enhances the impression that the nasal bones are likewise hyperplastic or clumsily constructed.

The peculiar nose form is one that is usually immediately and strikingly apparent. Figure 3, reproduced from Klein (1950), illustrates it in an extreme form. In infants, the beginning of this outgrowth is already apparent and is frequently asymmetrical. Obviously during embryonic development the median frontal process and portions of the two medial and lateral nasal processes have grown hyperplastic at the cost of the neighboring ocular regions, as I explained in a previous communication dealing with ptosis (Waardenburg, 1930).

[6] Van der Hoeve has seen solitary cases of dystopia canthorum with a variety of other ocular defects, such as: ptosis, epicanthus, paresis of M. recti superiores and nystagmus (1928, 1929), hypertelorism (1930, 1934), high myopia and dystrophy (coloboma?) of the macula lutea and papilla (1941), aniridia congenita (1944). In one of his cases only the upper lacrimal points were more displaced toward the lateral angle (1939). Halbertsma (1939) mentions the combination with microphthalmus, microcornea plana, microphakia, aniridia, and hypoplasia of the optic disc and retina.

Heterochromia iridum totalis sive partialis

The pigmentary defect of the iris which accompanies the syndrome has several noteworthy features. In the majority of the cases showing heterochromia iridum the lighter of the two irides was of a striking whitish-blue color of a form rarely encountered. Upon slit-lamp examination one gains the impression that the epithelial layer and the anterior covering membrane are normally developed, whereas the tissue leaf between them is very deficient, thus making the iris appear very thin and flat. There is no distinct partition between the two annuli of the iris, and I can well imagine that such eyes, when affected by chronic glaucoma, as in the proband of Pedigree 1, may speedily develop some form of secondary iris atrophy. In the numerous individuals showing the syndrome wherein both irides were blue, I was often impressed by a very similar appearance of hypoplasia of the iris stroma. In a few cases the choroid and fundus seemed to take part in the pigment defect in minor degree, but generally I was unable to detect a significant difference in pigmentation in the two fundi.

There were a few cases in which the aspect of pigmentation did not differ greatly between the two eyes and in which the lesser pigmented iris was not blue. Usually the cases of partial heterochromia showed blue sectors, sometimes in both irides at corresponding regions, sometimes in different regions. on the only cases showing a small dark sector in a blue eye, the other features If the syndrome were absent, so that I suspect such cases as having a different origin (*iris bicolor*). The latter anomaly is also known to occur as an inherited trait (Bond, 1912; Passow, 1932).

In the literature we seldom encounter familial or hereditary heterochromia iridum, although there are publications by Gossage (1907-1908), van den Breggen (1915), Matiegka and Brozek (1924), Kranz (1926), and Nowak (1932). Further discussion of the literature has been given elsewhere (Waardenburg, 1932, 1938). There are cases in concordant MZ twins, sometimes with mirrored asymmetry. Here again more extensive family studies will be needed to decide whether *heterochromia iridum simplex* occurs as a separate anomaly. I have found heterochromia mentioned once in connection with deafmutism, but without dystopia canthorum and other features of the syndrome: Walsh (1947, p. 412) cites a woman with heterochromia iridum whose one daughter has heterochromia and whose other daughter has congenital deafness. Van Gilse (1926) described a woman with total congenital deafness in one ear and partial deafness in the other. She had dark blond hair and rather light skin with a kind of freckling in certain skin areas, the latter trait being present in her mother as well. Her irides were brown but showed blue sectors in their upper portions. Nothing is mentioned regarding the eye regions, but it seems possible that this case may be an example of my syndrome, or related to it.

Leucismus pilorum (poliosis) or "white forelock"

It seems quite clear that this feature of the syndrome is not peculiar to it, but that a white forelock may be inherited as a separate entity. There are numerous published illustrations of this form of *albinismus circumscriptus pilorum* in which we see not the slightest indication of dystopia of the medial canthi and where we find no mention of heterochromia iridum or deafmutism. I personally know a family in which 5 sibs show a distinct white hairlock; in the mother and maternal grandmother the anomaly consisted of only a few white hairs in the midline, but in the great-grandmother the anomaly was again a conspicuous one. In this family the defect was characterized by its association with circumscribed hypopigmented areas on the trunk and extremities, a feature not usually found in the above-described families with the new syndrome. Presumably we are dealing with manifestations of different genes.

Mazzini (1924), supplementing an earlier report by Rizzoli (1877), described two first cousins showing both circumscribed albinism and congenital deafness. These individuals, who figured in the *6th* generation of a large pedigree in which a white hair lock and leucistic skin spots were transmitted through 8 generations, were the only members reported as deaf. They died at the ages of 8 and 17, respectively. Five photographs of affected members of this family are presented, and there is no evident anomaly of the eyelids. The iris color was reported as normal in the examined individuals. The deafmutism may therefore be a casual complication in this pedigree, although Mazzini is inclined to assume a common sympathetic nervous origin and draws a comparison with the combination of deafness and pigment anomalies in animals. Also, attention should again be called to Klein's (1947, 1950) case of generalized leucism exhibiting all of the other features of my syndrome, excepting heterochromia, and with additional abnormalities of the musculature and skeleton. It may be that the blue irides in this case represent a generalized bilateral hypoplasia iridis, as was suggested in some of my own cases.

Without laying much stress upon the association, Hammerschlag (1907) and Urbantschitsch (1910) both mention heterochromia iridum and partial albinism among the complications of deafmutism in man. Hammerschlag (1908) even describes a very complicated case combining deafness with heterochromia and partial albinism of the head hair. Hanhart (1938) found nothing of this kind in Switzerland, nor did Lindenow (1945) in his Danish cases. Ingeborg Kling (1932) found an albinotic fundus in 1.9% of 304 deaf school children in Sweden; one of these suffered in addition from a generalized albinism, microphthalmus and mental retardation.

A remarkable 4-generation pedigree was published by Mende (1926), which undoubtedly belongs to my syndrome. In this kindred, residing in Berlin, deafmutism was frequently combined with evidences of leucism, such as white

hairlock or poliosis of the eyebrows, cilia or beard, or with leucistic skin spots on the back, arms, legs, hands and feet, and with hyperpigmented regions. Calling the condition "deafmutism with a mongoloid tendency" the author repeated the common mistake of confusing the blepharophimosis which results from lateral displacement of the inner canthi with the form occurring in mongolism. The description of the nose root and eye region and a photograph of an affected boy furnish conclusive evidence for dystopia canthorum. Even the growing together of the eyebrows is present. Curiously, the eye color is not mentioned in any of Mende's cases; presumably a heterochromia if present in any individual was not striking. Two deafmute sibs in one branch of the family showed a disturbed vestibular function. Some members of the family exhibited only the eyelid anomaly.

Ellis (1931) mentions the case of a 7 year-old boy whose right iris was brown and whose left iris was greenish blue. On the side with the brown iris there was a 6 cm.-wide patch of black hair on an otherwise fair head of hair. This combination is just the opposite of that which characterizes my syndrome, where the hypopigmented areas of the hair and the iris are the abnormal ones. Ellis' case suggests a kind of melanosis, whereas the case of Stannius mentioned in the discussion of Ellis' paper corresponds more with my observations. His patient displayed a depigmented left lower quadrant of the right iris combined with a local poliosis of the cilia of the lower lid, a white tuft of hair on the head and a white spot on the cheek.

I have not had the opportunity to examine many patients undressed. In one case (ped. 10, *III-43*) I found a leucism of the skin of the forehead and in a few other cases (peds. 5 and 13) there were depigmented spots noted elsewhere, but this question deserves more intensive study in future work. At present, however, the observations of Mende, Klein, Stannius and myself suggest an occasional major extension of the leucism beyond the usual area affected in the head hair.

As I have noted in the descriptions of several families (peds. 1, 6, 9, 12), it seems possible that premature greying may represent an equivalent of white forelock in some individuals.

Surditas congenita (*Surdimutitas*)

Deafness and deafmutism may be due to hereditary (endogenous) and non-hereditary (exogenous) factors. Endogenous deafmutism is practically always a result of hereditary defect or disposition, and not of hormonal disturbance. We recognize nowadays several different recessive as well as dominant types:

A. *Recessive types.*

1. *Connatal sporadic deafmutism* is so-called because often without known cause only one child in a seemingly healthy family is afflicted. There is, how-

ever, a high proportion of consanguinity of the normal parents even in such solitary cases. Histologically the functional anomaly is due to a dystrophy or atrophy of the sense elements in the acoustic labyrinth, either a primary one or a secondary one following aplasia or dysplasia of the stria vascularis. Whereas as a rule the sense elements of the sacculus are also affected, the vestibular function and equilibrium are usually intact, because the pars superior of the labyrinth is undamaged. A common opinion about the primary or secondary role of occasional changes in the auditory pathways of the brain (Brouwer, 1909, 1910) is still lacking. All cases show peripheral defects. The organ of Corti is rudimentary or entirely undeveloped, and the N. cochearis has little or no nerve fibres and ganglion cells. The bony part is normal. The drum membranes are usually normal but may be dull or damaged if such patients have suffered from otitis media. In many cases a trace of hearing may persist, and this may often be symmetrical in the two ears, in contrast to acquired deafness where there is usually an asymmetrical defect. However, exceptions occur in both directions, so it is impossible to use this criterion for a definite decision between hereditary and acquired deafmutism. But a genetic defect becomes more probable if symmetric remnants of hearing are found in two or more members of the same family.

There are also recessive types of labyrinthine deafness wherein the abnormal gene is retarded in its action, so that the age of onset may be 3 years or older (Boonacker, 1915) or 8 years and older (de Kleyn, 1915). In such cases the deafness is of course not followed by mutism.

2. Another type of recessive deafness or deafmutism may be combined with disturbed vestibular function (Müller, 1936; Loebell, 1938).

3. Deafness or deafmutism without vestibular dysfunction may evidently be caused by still another recessive gene, as is deduced from the fact there are instances of deafmute couples, both of whom arose from consanguineous matings or have deafmute sibs, who have produced all normal offspring (Fay, 1898; Hammerschlag, 1910; de Wilde, 1913; Mühlmann, 1930; Csørcz & Tokay, 1934; Lindenov, 1945; Lehmann, 1950).

4. Deafness or deafmutism is known to be combined with dystrophia retinae pigmentosa or punctata albescens (Usher's syndrome). There is a high frequency of parental consanguinity in these cases. It is evidently due to a polyphenic recessive gene with varying degrees of penetrance of the constituent symptoms. That the gene must be distinct from the more common one(s) for sporadic deafmutism is demonstrated in Lindenov's (1945) pedigree No. 55; a deafmute man whose parents were related and who had 3 deafmute sibs and 1 normal sib produced a normal daughter in a mating with a woman who, like 2 sisters, showed Usher's syndrome. Deafmutes with Usher's syndrome, as pointed out by Lindenov, have disturbances of equilibrium in the form of a swinging gait, especially in darkness. One would expect therefore an

alteration of the vestibular part of the labyrinth, but the anatomical findings in no way deviate from those in sporadic deafmutism (Siebermann & Bing, 1 case; Alexander, 1 case; Nager, 2 cases). Van der Hoeve (1913) reported vestibular disturbances in 3 sibs suffering from Usher's syndrome and also found partial albinism in one of these cases and in two other sibs lacking the syndrome; the albinism was therefore evidently due to homozygosity for a second recessive gene resulting from this consanguineous marriage.

B. *Dominant types.*

1. One type of dominantly inherited deafmutism represents an extreme variant of dominant labyrinthine deafness (Albrecht 1923, 1926). The latter usually develops in adulthood, but since the age of onset and severity is very variable within affected families, some members may become deaf at such an early age that deafmutism results (pedigrees of Albrecht, 1923, 1926; Schneider, 1937; Müller, 1936; Lindenov, 1945). Müller's pedigree is particularly interesting because this form of dominant early deafness is represented by deafmutism with vestibular disturbance in different generations. Grohmann's (1939) pedigree which has often been cited as an example of normal progeny resulting from two recessive parents, is not plainly proved as such, and may possibly belong here; so many cases of hardness of hearing occur among the paternal relatives that a dominant type of defect cannot be excluded.

The histological picture shows a hypoplasia of the bony cochlea, and particularly of the modiolus. Also, a more or less defective cochlear nerve is found, and there are alterations of the sense elements and of the sacculus. The semi-circular canals and the utriculus are normal. The organ of equilibrium is usually not disturbed. In contrast to acquired labyrinthine deafness, where initially the upper tone limit is markedly lowered, in the dominant hereditary form the upper limit is but slightly lowered and the lower limit somewhat raised. There is a greater deficiency in bone conduction than in air conduction, in contrast to otosclerosis.

2. In 1937 Vogelsang *et al.* published a pedigree with 6 persons suffering from dominant labyrinthine deafness in 3 generations. In one sibship 3 members have inner ear deafness and one is a deafmute; in all four of these cases there was an associated dystrophia retinae pigmentosa and all but one case was feebleminded. This seems to be the dominant counterpart of Usher's syndrome. The histopathology is not yet known.

3. We may now add a third category, namely the irregularly expressed dominant deafmutism identified with the syndrome described in this paper. It will be most interesting to learn whether the otologist will be able to discover distinguishing clinical and histological features for this type of deafness.

4. It seems not at all unlikely that still other dominant forms of congenital deafness or deafmutism may exist, and the following pedigree based upon one of my experiences in the present study is suggestive of this.

PEDIGREE 15. (FAMILY MA, FIG. 28)

III-1. (*Probandus*, J.M.). This 8 year-old deafmute boy was an inmate at Amsterdam, the son of two congenital deafmutes. The nose root is prominent, and there is a marked bilateral epicanthus. The irides are blue. There is no distinct dystopia canthi medialis (interocular dimensions: 34-52-78), but the lacrimal points reach almost to the limbi corneae. There is some extraocular muscle disturbance, the left eye turning upwards and lagging behind the right eye on looking to the right. The gait is abnormal, the forelegs performing with exaggerated dorsiflexions at the knee joints. Both external ears are malformed, with missing upper portions; the helices are broad and flattened and their upper borders project at right angles to the head. The mandible is of normal size.

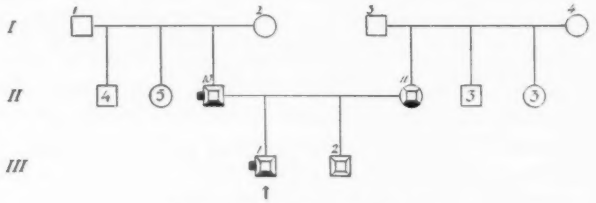

FIG. 28. Pedigree 15, Family Ma

III-2. A younger brother, aged 5, is quite normal. (Interocular dimensions: 32-50-77).

II-10, the father, aged 36, is a congenital deafmute showing a protruding left eye with a retracted upper lid, giving the impression that there might have been performed a tenotomy of M. rectus medialis, although actually no operations on the eyes had ever been performed. The irides are greyish-blue. The root and bridge of the nose are high, but there is no definite dystopia canthorum (interocular dimensions: 36-56-85). The right lacrimal point is displaced to a point nearly opposite the inner limbus, while the left point is well medial to the limbus. The outer ears are malformed, exactly as in the probandus.

II-11, the mother, aged 35, shows no eye anomalies, but is a congenital deafmute.

Comment: Both the father and the mother of this case have a number of reportedly normal sibs, but I was unable to examine these people. Neither parent was the result of a consanguineous marriage, nor is deafness known in any other member of the family. While I do not believe that the deafness in father and son is assignable to the present syndrome, I am frankly puzzled as to the genetic explanation of events in this family. Both deaf parents could not possess the same type of recessive deafness, since they have a normal son, but their affected son may owe his defect to perhaps a special dominantly inherited form, or else, we may be dealing with two recessive forms of deafness and a mating of the rare type *aaBB* × *Aabb*. It is, of course, possible that the mother's deafness, reportedly congenital, may represent a type acquired through early post-natal infection; but in any case I am inclined to assume some kind of dominant inheritance in the father and son, where the deafness is associated with a deformity of the external ear.

Pigmentary abnormalities and deafness in other mammals

It is a well known fact that many "color genes" in rodents and other mammalian species are not wholly "neutral" but have an influence on metabolism, behavior, and other fundamental physiological and developmental processes. Particularly interesting in relation to the newly described human syndrome

are those mammalian mutations causing syndromes which include pigmentary anomalies and deafness with or without locomotor disturbances.

In *Mus musculus*, for example, a so-called *varitint-waddler* type has been described by Cloudman and Bunker (1945). It includes the triad of circling about an axis, involuntary head movements and deafness (apparent soon after birth), and a pigmentary defect in the fur. Heterozygous animals show irregular spots of white hairs on the head and body or a sprinkling of white hairs between dark hairs, giving a roan effect. Later the darker areas gradually fade, so that the mouse becomes quite white. They swim easily, but do so in tight circles. Homozygotes for the abnormal gene exhibit most of the features of the syndrome in a more severe form. This same triad, including early deafness, occurs, in fact, in a number of mutant mouse types variously named in accordance with the kind of locomotor disturbance produced: waltzer (so-called Japanese), shaker-1, shaker-2, jerker, kreisler, pirouette, dervish. Grüneberg (1947) remarks that this triad has no close parallel in man.

It is also well known in mammalian genetics that some genes affecting the pigmentation of the fur also affect the iris. In the rabbit, for example, the recessive "Vienna blue-eyed white" gene produces a white coat with depigmentation of the iris (glass eye). The same applies to the recessive Dutch-spotted rabbit, where the extremely white animals show "glass eye," while animals with less white show a total or partial heterochromia iridum. The latter does not occur in the dominant English-spotted rabbit. According to Klemola (1931) a similar recessive form of piebalding with glassy eye occurs in the horse. Grüneberg notes that the iris may take part in various spotting factors known in rodents, causing a heterochromia, and that some spotting genes also reduce the choroidal pigment (e.g. in deaf dancing-mice). There are also in cats and dogs a number of interesting observations relating to the combination of pigmentary defects of the eyes and hair with congenital deafness.

Darwin (1885) knew that white cats with blue eyes were commonly deaf, and other investigators have noted congenital or early developed deafness in animals with variegated eye colors. It is not recorded whether such animals exhibit the abnormalities of the ocular adnexa seen in the new human syndrome. The Dalmatian dog, whose skin is spotted and whose eyes are sometimes variegated in color, is not uncommonly deaf, and the same is true of the Siamese cat, with its albinotic coat and heterochromia iridum.

Abelsdorff (1904) studied the eyes of a deaf dog with blue irides. He found no mesodermal pigment in the iris, ciliary body, or choroid; in all other respects the eyes were normal.

Alexander (1900) and Alexander and Tandler (1905) performed histological studies of the auditory organ and especially the inner ears of partially albinotic cats and of congenitally deaf cats and dogs. Finally, Alexander examined the inner ear in one of two deaf white cats having mixed blue and brownish-yellow irides. In all of these animals the mesodermal pigment of the perilymphatic cells, which corresponds in all ways with the pigment of the choroid, was lacking. In the above-mentioned two cats, Alexander and Tandler found bony

alterations of the modiolus and membranous changes in the labyrinth, without marked alteration of the spiral ganglion or cochlear nerve. Although these authors reported no changes in the brains of these deaf cats, Rawitz (1896) found a marked decrease in the first and third temporal gyri and a generalized hypoplasia of the entire temporal lobe.

Lauber (1906) examined the eyes of the two above-mentioned deaf white cats in one of which Alexander had studied the auditory organ. He found that the lighter eye in each cat lacked uveal pigment throughout and concluded that heterochromia iridum was part of a more extensive localized albinism depriving these animals of pigment both in the uvea and in the perilymphatic mesoderm, in contrast to normal blue eyes in which there is pigment in the choroid.

Przibram (1908) observed heterochromia iridum in three families of cats through 2 and 3 generations; in each case the heterochromia was associated with unilateral deafness occurring on the side with the lighter iris. Matings of two heterochromic cats produced isochromic as well as heterochromic offspring. The same was true for matings of heterochromic cats with either blue-eyed cats or yellow-eyed cats.

Nachtsheim (1935, 1940) states that German (tiger) bulldogs and Norwegian Dunkerdogs with piebald skin often show partial or total heterochromia iridum due to a heterozygous genotype. In homozygous condition the same gene produces deafness as well as blindness (Wriedt, 1919, 1925; Mohr, 1926, 1929; cited by Nachtsheim).

Histological research in animals has not yet yielded definite conclusions about the localization of the primary malformation. Although more or less extensive degenerative changes have been found in the brains by various investigators (Rawitz, 1896, and Winkler, 1900, in the cat; Kuiper, 1913, in waltzing mice; Zimmermann, 1935, in shaker mice) one is not yet permitted to generalize and assume a primary central origin for all cases. A number of other authors have found only peripheral changes (Alexander, 1900, in a cat; Van Lennep, 1910, in waltzing mice; Lurie, 1939 and 1941, in dancing guinea pigs; and Van Gilse, 1942, in shaker mice). Quix (1910) assumes the central brain lesions to be secondary to the peripheral organ changes in man as well as in animals. It seems likely that both types, with primary central and primary peripheral origins, may exist.

In a publication by van Gilse, Hinnen and Nieuwenhuijse (1942, p. 386) we find this remark made by Miss Nieuwenhuijse: "In human beings, also, the possibility of a correlation between labyrinthine deafness and pigmentation anomalies may be considered." She then refers to two families observed by van Gilse in which severe deafness and pigment spots of the iris as well as abundant freckling occur in two generations. She points out, however, that van Gilse cautioned against the danger of *false correlations* and concluded that "heterochromia, for example, is in human beings certainly not connected with deafness." Obviously this opinion seems now to have been invalidated, and the combination of anomalies demonstrated to occur in the new human syndrome seems to establish a firm link to certain facts long known in other mammals.

SOME REMARKS ON THE PHENOGENETIC MECHANISM

Although the study of similar syndromes in other mammals may eventually assist in explaining the human syndrome just described, no definite clues seem to be afforded at the present time. It might be pointed out, however, that

there is no necessity of looking for a distinct temporal phase in which all symptoms may arise together. Although such a causal synchronism may occur in some syndromes such as dysostosis mandibulofacialis (Treacher Collins, Franceschetti-Zwahlen-Klein) or in the combination of stiff ptosis, epicanthus, blepharophimosis, and dystopia canthorum (Waardenburg), as I was able to show embryologically, there are many other syndromes presenting anomalies arising at different times (e.g. Marfan's syndrome). Moreover, a critical phase in embryonic life governing the development of pigment in the skin, hair, and eyes is unknown.

No one has yet explained the way in which heterochromia iridum simplex arises. We are merely pronouncing a *testimonium paupertatis* in saying that a heterochromic is a heterozygous individual in whom, for unknown reasons, the one allele is expressed on one side, the other on the other. The cause of the mosaicism could lie in peristatic differences in the two body halves, but it is also possible that the variegation may arise from some kind of somatic genetic segregation, as would seem more likely in the case of circumscribed albinism of the kind showing an irregular distribution over the body, though perhaps not for the kind restricted to the midline of the forehead. In either case, the process could be governed genetically by the action of an abnormal gene in heterozygous condition, the existence of which we must assume in the case of the newly described syndrome.

The question arises whether the circumscribed leucism of skin, hair and iris might be in some way related to Bremer's *status dysraphicus* due to an insufficient closure of the neural groove. Passow (1933) assumed this to be true for certain complicated forms of heterochromia iridum, such as that resulting from unilateral sympathetic paralysis with pupillary and other changes and for heterochromia combined with cataract, descemetitis, cloudiness of the vitreous, and glaucoma. He stated flatly that no such association holds for heterochromia iridum simplex. His conclusion, however, was based on only three cases of the latter anomaly which were negative for symptoms of the dysraphic state. I was unable to examine in detail the majority of the members of my present series of families in this respect, but in all cases where this was done, my findings were also negative. The only cases which might possibly be viewed with suspicion were three heterochromics having the syndrome, one showing anisocoria of the lighter iris (ped. 5, *IV-12*), one showing an unusual arm span (ped. 10, *III-33*), and one case of bilateral cleft lip and palate (ped. 10, *III-38*). In this connection we may recall Walsh's cases (which I believe to be examples of the new syndrome, although probably without heterochromia) wherein both affected sibs showed a nearly complete absence of the uvula, and Klein's case showing cleft palate. Hanhart (1938, family D) describes a probable dysraphic status in a mentally retarded boy showing generalized infantilism, with *iris bicolor* and a small palpebral fissure of the right eye.

Also, Mende (1926) mentions a case of deafmutism in brother and sister, the sister showing a rudimentary cleft lip and the brother a narrow high palate, and another case of harelip in a normal hearing boy whose sister and mother were deafmutes.

It would seem that the time is not ripe to delve deeper into the question of the phenogenetic mechanism or to attempt to solve various other genetic and embryological problems posed by the new syndrome. This must remain a program for the future. In the meantime, it is hoped that workers in other countries will seek to confirm my findings and to ascertain with what frequencies the syndrome occurs there.

SUMMARY

A new syndrome is described, consisting of (1) lateral displacement of the medial canthi and lacrimal points, (2) a hyperplastic, broad, high nasal root, (3) hyperplasia of the medial portions of the eyebrows, (4) partial or total heterochromia iridum, (5) congenital deafness or partial (unilateral) deafness, and (6) circumscribed albinism of the frontal head hair (white forelock).

Among 840 deafmutes in five Dutch institutes for the deaf, 12 cases of the new syndrome were discovered. From detailed studies of the families of these and other probands, it is evident that the syndrome shows dominant autosomal inheritance. The several component anomalies exhibit varying degrees of penetrance, the order of decreasing penetrance being probably (1) → (6) as listed above.

It is estimated that about 1.43 per cent of all deafmutes in the Netherlands owe their deafness to the irregularly expressed dominant form occurring in this syndrome. This amounts to a population incidence of 1 per 212,000, but since the penetrance of the deafness component is low (about 20 per cent), the incidence of the syndrome as a whole (with or without deafness) must be considerably higher (about 1 per 42,000 population).

Five out of 16 probands having the syndrome are apparently sporadic cases. Assuming them to be new mutations leads to a mutation rate estimate of 1 per 270,000 gametes.

In addition to the Dutch cases, there are reports in the literature suggesting that the syndrome also exists in the United States, Switzerland, Italy, and Germany.

The literature is surveyed with special reference to the genetics of the separate anomalies and their combinations as observed in man and in other mammals, and a brief discussion of possible phenogenetic mechanisms is appended.

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Some Statistical Problems Posed by Waardenburg's Data on Dystopia canthorum and Associated Anomalies

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P. J. WAARDENBURG'S monograph published in the current number of the *Journal* is one of exceptional interest for otologists and ophthalmologists. The fact that a "new" form of congenital deafness, accounting for about 1.5 per cent of all cases of deafmutism in the Netherlands, can now be identified by means of several peculiar morphological anomalies with which it is associated to form a dominantly inherited syndrome marks an important advance in the study of deafness. No doubt many workers will wish to undertake further study of this complex and it therefore seems desirable to examine in greater detail certain statistical problems posed by the extensive body of genetic data recorded. Some of these questions are of a more practical kind, being concerned with the discreteness of the syndrome and with means of identifying it. Others are more theoretical, but may have some significance from the point of view of the physiological or cytogenetic mechanism.

As defined by Waardenburg, the syndrome in question includes: (1) *dystopia canthi medialis lateroversa*, i.e. lateral displacement of the inner angles of the eyelids, (2) a broad high nose root, (3) hyperplasia of the medial portions of the eyebrows, (4) heterochromia iridum, (5) white forelock, and (6) congenital deafness. The syndrome as a whole appears to be transmitted as a dominantly inherited complex in the majority of Waardenburg's families. Each constituent anomaly is manifested in only a portion of the assumed heterozygotes, the penetrance being least (about 20 per cent) for deafness and white forelock. However, the eyelid defect—hereinafter abbreviated d.c.m.l.—appears to be almost constantly present in relatives having one or more of the other anomalies and shows in itself a pattern of inheritance typical of a dominant abnormality with full penetrance. This defect therefore promises to be of greatest value for diagnosis of the syndrome and for predicting which members of a family may be capable of producing deaf children.

Special interest therefore attaches to the *interocular measurements* recorded by Waardenburg in almost all examined members of his several kindreds. These consist of the distances between the inner canthi (*a*), the pupillary centers (*b*), and the outer canthi (*c*). It should be emphasized that the diagnosis of d.c.m.l. need not be based solely on these measurements, for there are other features, such as displacement of the lacrimal points, difficulties of lacrimal

conduction, and size and shape of the lid fissures (measurable in other ways), which may assist in making the diagnosis. Nevertheless the 3 measurements probably summarize much of the relevant information and they are objective and easily made. We may therefore content ourselves with them and ask in relation to Waardenburg's data a series of questions, of which the first would be: which of the three measurements are altered in individuals showing the syndrome, and in what way?

Table 1 lists certain statistics calculated from the data presented in the aforementioned monograph (Waardenburg, 1951). Accepting the author's classification of individuals showing the syndrome (W) or lacking it (N, "normals"), I have restricted the analysis to 70 individuals, including 45 members of W and 25 members of N, belonging to 20 sibships. This includes all sibships having at least one member with the syndrome and having interocular measurements recorded for *all* examined members of the sibship. (In some cases, including several large sibships of pedigree 11, Dr. Waardenburg made no record of measurements for individuals classed as "normal"; since this might introduce biases, I have excluded such sibships from table 1, but the affected sibs will be utilized for other purposes.) At a later place (fig. 2) the particular sibships used here will be identified by Waardenburg's pedigree numbers, so that those wishing to reexamine the problem may readily reconstruct the data from Waardenburg's paper.

TABLE 1. INTEROCULAR MEASUREMENTS IN INDIVIDUALS HAVING OR LACKING SYNDROME INCLUDING DYSTOPIA CANTHORUM

Data summarized include 20 sibships from Waardenburg's families, selected as described in the text.

a = inner canthal diameter, b = interpupillary diameter, c = outer canthal diameter

STATISTIC		SYNDROME (W)			NORMALS (N)			DIFFERENCES (W − N) OR F-RATIO (BOTH SEXES COMBINED)
		Males	Females	Total	Males	Females	Total	
Number	n	28	17	45	12	13	25	
Means (mm.)	$\bar{a}$	42.79	42.79	42.79	32.21	32.00	32.10	$d_a = 10.69$**
	$\bar{b}$	62.70	61.74	62.33	62.71	59.96	61.28	$d_b = 1.05$
	$\bar{c}$	85.82	84.65	85.38	87.25	83.85	85.48	$d_c = -0.10$
Variances (mm.²)	V_a	15.32	15.22	14.94	7.88	9.67	8.46	$F = 1.766$
	V_b	17.34	20.50	18.32	33.93	28.94	31.98	$F = 1.746$
	V_c	24.37	21.37	23.06	54.20	53.64	54.68	$F = 2.371$*
Correlation coefficients	r_{ab}	0.520	0.773	0.614	0.831	0.904	0.847	$\delta = -0.233$
	r_{ac}	0.505	0.841	0.620	0.787	0.739	0.746	$\delta = -0.127$
	r_{bc}	0.733	0.952	0.816	0.874	0.856	0.873	$\delta = -0.057$

** Difference highly significant ($P < 0.01$). * F-ratio significant ($P < 0.05$).

Referring now to the table, it is seen that individuals possessing the syndrome have inner canthal diameters averaging over 1 centimeter greater than those of their normal sibs (d_a = 10.69 mm.). The estimated variance of a is greater among persons showing the syndrome, although the excess is not quite significant (F = 1.766). By contrast, the means for the interpupillary and outer canthal diameters are not significantly different in the two classes; here the observed variances are greater in the N group, and the difference in V_c could be judged significant. For the present, however, it seems best to conclude that the only definite change lies in the increased inner canthal dimension and that the anomaly is thus fully described by the title "d.c.m.l." However, the fact that the two phenotypes are not differentiated by b and c does not mean that these two measurements are without value in discriminating the two phenotypes. If we plot the inner canthal diameters by sibships (as will be done later for a function of all 3 measurements) the measurement a in itself is seen to be a very good "discriminant function," showing a markedly bimodal distribution. But naturally some young children having the anomaly will have values of a smaller than those of some normal adults. Obviously some means of adjusting the inner canthal distance for concomitant age or general body-size variation is needed, and there are reasons for suspecting that the two additional interocular dimensions, each being highly correlated with a in both phenotypes, might be more useful than age.

A DISCRIMINANT FUNCTION FOR DYSTOPIA CANTHORUM

Although the variances in a, b and c are somewhat unequal in the two classes, the significance of the inequalities is doubtful and we may therefore apply Fisher's (1936) classical discriminant function technique, which is appropriate to comparisons of two groups having equal variances and covariances in several variates. The method consists in choosing a linear function of the three measurements

$$L'' = \lambda_1 a + \lambda_2 b + \lambda_3 c$$

for which the ratio of the variance between classes (phenotypes W and N) to that within classes is maximal. The λ's are found by solving the equations:

$$\begin{aligned} \lambda_1 S(a^2) + \lambda_2 S(ab) + \lambda_3 S(ac) &= d_a , \\ \lambda_1 S(ab) + \lambda_2 S(b^2) + \lambda_3 S(bc) &= d_b , \\ \lambda_1 S(ac) + \lambda_2 S(bc) + \lambda_3 S(c^2) &= d_c , \end{aligned}$$

where $S(a^2)$, $S(ab)$, etc. are the sums of squares and products of deviations from means within classes (pooled for W and N) and d_a, d_b and d_c are the mean differences in the 3 variates, as defined in table 1. For the present data, we find

$$L'' = 0.022448a - 0.0056045b - 0.0047572c \text{ mm.}$$

In order to have the coefficient of a equal unity, we multiply each term by $1/\lambda_1$, (the maximized ratio of the variances between and within classes is of course unchanged) with the result:

$$L' = a - 0.2497b - 0.2119c \text{ mm.}$$

At this point it is of interest to remember that a, b and c are overlapping distances measured on a single straight line. If we wish to consider the three non-overlapping intervals a, $(b - a)$ and $(c - b)$, we may write L' in the form

$$L' = 0.5384a - 0.4616(b - a) - 0.2119(c - b)$$

and note that approximately equal weight is assigned to a decrease in $(b - a)$ as to an increase in a. Alternatively, we may write

$$L' = 0.5384a - 0.2497(b - a) - 0.2119(c - a),$$

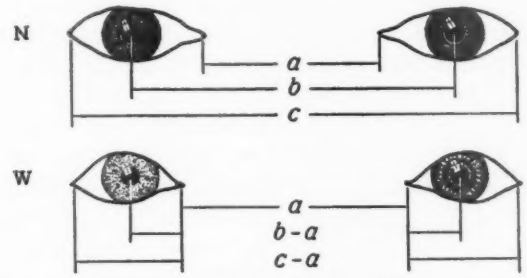

FIG. 1. Interocular proportions for syndrome (W) and normal (N).

showing that we may consider the compound L' as measuring, for both eyes, the horizontal displacement of the inner canthus from three points: a midpoint on the nose bridge, the pupillary center, and the outer canthus (fig. 1). In a rough way, then, we could say that L' measures three interrelated changes:

increase in a	"broad nose root,"
decrease in $(b - a)$	"concealment of the nasal half of the sclera,"
and decrease in $(c - a)$	"blepharophimosis,"

these making up 54, 25 and 21 per cent of the total change, respectively.

For diagnostic purposes it may be convenient to use in place of L' a function which uniformly tends to assign positive scores to members of W and negative scores to members of N. On the assumption that L' is normally distributed in both populations W and N, the isocritic point, defined as that value of L' for which the probability of origin from population W is equal to the probability of origin from population N, is given by

$$\frac{\Lambda_W \sigma_N + \Lambda_N \sigma_W}{\sigma_W + \sigma_N},$$

where Λ_W and Λ_N are the means and σ_W and σ_N are the standard deviations in the two populations. Now, the observed means and standard deviations of L' are found to be:

$$\bar{l}'_W = +9.133, \text{ and } s'_W = \pm 2.956 \text{ for the 45 members of W;}$$
$$\bar{l}'_N = -1.315, \text{ and } s'_N = \pm 1.699 \text{ for the 25 members of N.}$$

Using these values, we could select an isocritic point at 2.498. However, since Fisher's linear discriminant assumes, for all measurements, equal variances and covariances in the two populations, and although the observed difference in variance of L' is significant, I have chosen to disregard the latter and to therefore subtract from L' a constant quantity $\frac{1}{2}(\bar{l}'_W + \bar{l}'_N) = 3.909$ mm., giving, as the final form for the discriminant function:

$$L = a - 0.2497b - 0.2119c - 3.909 \text{ mm.}$$

This is the function adopted as a basis for the following discussion.

In figure 2 the values of L are plotted for the 70 individuals used in deriving the function. Obviously the trait d.c.m.l. may be regarded as a distinct segregating anomaly; the distribution is markedly bimodal and this is consistently shown in the individual sibships. In no case does the L-value dispute the classification made by Dr. Waardenburg. In particular, it will be seen that the probands of pedigrees 4 and 8, regarded by him as examples of the syndrome and so used here in constructing the discriminant function, are definitely normal with respect to the anomaly d.c.m.l. If it be supposed that they possess the same genetic factor responsible for the other cases of the syndrome, they therefore require the postulation of a "lack of penetrance" of this feature, and it is curious that no example of this is found among the sibships segregating for the anomaly.

There is an excess of W individuals in the 20 sibships of figure 2, as of course would be expected in consequence of selecting sibships having at least one affected member. We are not here concerned with testing the 1:1 segregation in these sibships. However, the possibility that this selection might also bias the results in the direction of an exaggerated bimodality in the distribution of the L-values might be considered. Most sibships include a proband possessing deafness as well as d.c.m.l. However, as will be shown later, W members with deafness do not in general have values of L exceeding those found in their affected sibs lacking deafness.

Figure 3 shows the same clear-cut separation of phenotypes in the measured parents of cases having the syndrome. The three pairs of normal parents (families 3, 7 and 13) correspond with the 3 sibships shown in figure 2; two of these consist of sporadic or isolated cases (probands 3 and 13), while the third sibship (family 7), containing 3 affected and 3 normal children derived

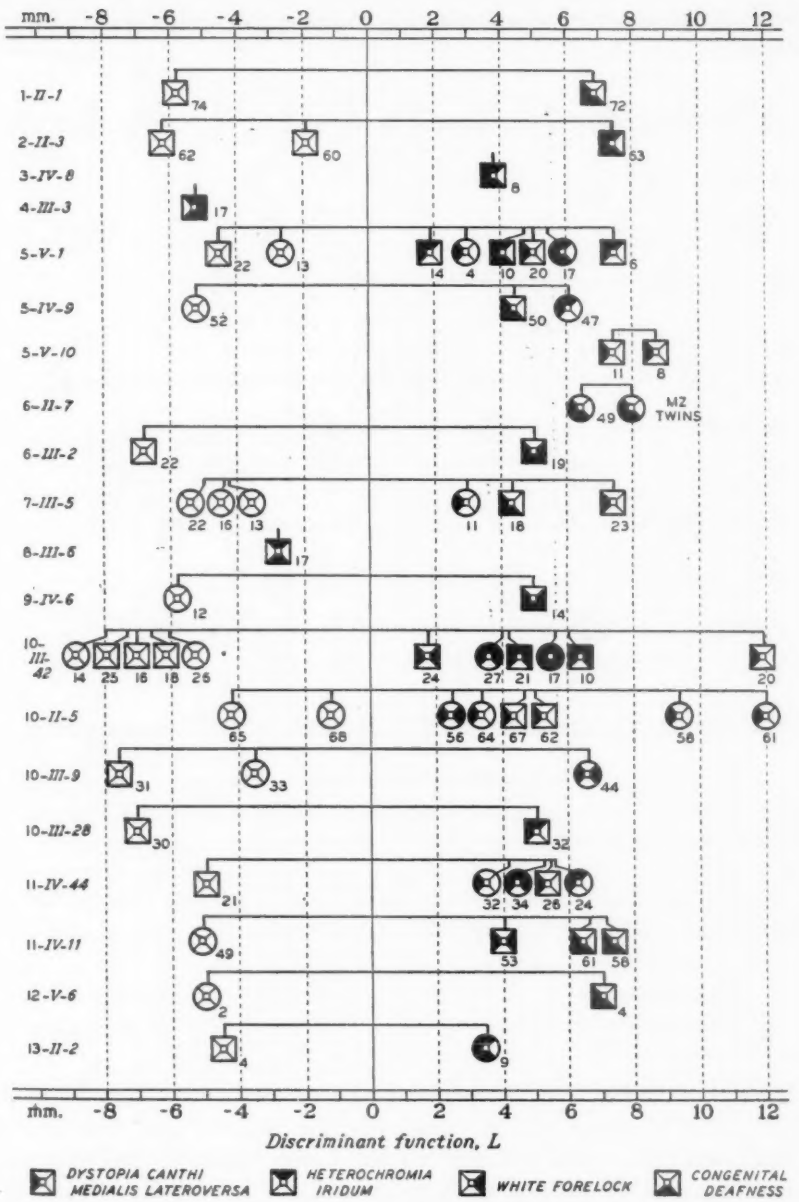

FIG. 2. Distribution of the linear discriminant L within the 20 sibships used in constructing the function. Waardenburg's pedigree and individual number is used to identify the first (leftmost) individual represented in each sibship. Numbers beneath the squares and circles are ages, in years

from normal parents, represents the only finding of this kind in Waardenburg's study.

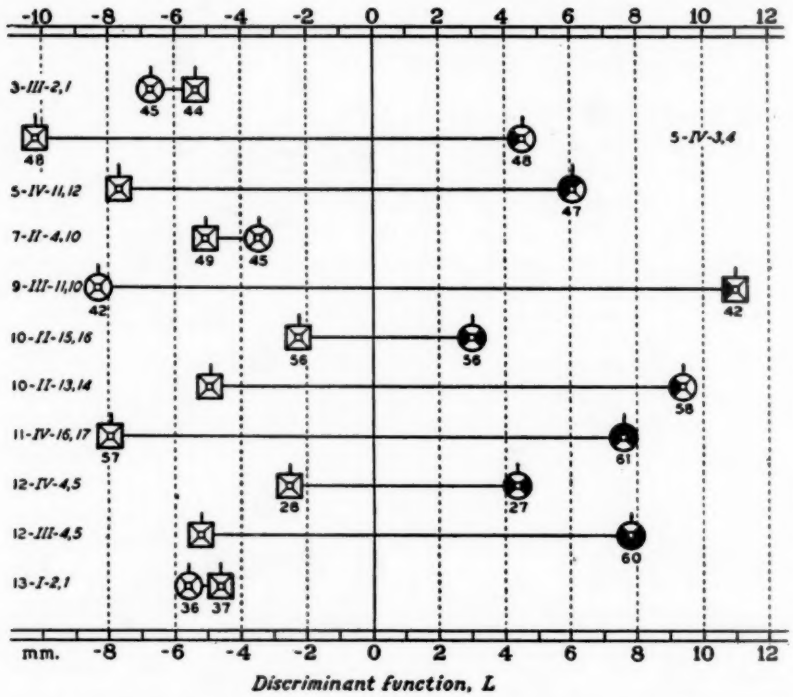

FIG. 3. Distribution of the discriminant L in the measured parents of individuals possessing the syndrome. Symbolism as in fig. 2.

Quantitatively, the distinctness of the anomaly d.c.m.l. is brought out in the following analysis of variance of the L-values:

Variation in L	*D.F.*	*Sum of Squares*	*Variance*	
Between phenotypes (W *vs.* N)	3	1754.23	584.743	$F = 82.92^{**}$
Within phenotypes	66	465.41	7.052	

The ratio of the two sums of squares, 1754.23/465.41 or 3.77, may be taken as a measure of efficiency of the chosen function. This compares with a ratio of 2.13 found upon using the inner canthal diameter alone (a) and with 3.24 found by use of the ratio of the inner canthal and interpupillary diameters (a/b).

To show that all 3 measurements, a, b and c, contribute significantly to the discriminant L, we may introduce a dummy variate, z, with scores

$$z = \frac{n_N}{n_W + n_N} = +\frac{25}{70} \text{ for members of W}$$

and

$$z = \frac{-n_W}{n_W + n_N} = -\frac{45}{70} \text{ for members of N,}$$

and compare the partial regression coefficients of z on a, b and c with their standard errors (cf. Fisher, 1936; Bartlett, 1951):

$$+0.07566 \pm 0.00493, t = 15.35;$$
$$-0.01889 \pm 0.01102, t = 1.71;$$
$$-0.01603 \pm 0.00858, t = 1.87.$$

Actually, the coefficients for b and c have t-values somewhat less than the value needed for significance at the 5 per cent level ($t = 2.00$, d.f. = 66), but we may conclude that b and c taken together have effected a significant improvement over the use of a alone, as is shown in the following analysis:

Variation in z	*D.F.*	*Sum of Squares*	*Variance*	*F*
Regression on a (partial)	1	12.0568	12.0568	236.14**
Regression on b and c	2	0.6448	0.3224	6.31**
Remainder	66	3.3698	0.05106	
Total	69	16.0714		

APPLICATIONS

Figure 2 shows how the values of L are distributed with respect to individual sibships, sex, age, and presence or absence of three other anomalies comprising the syndrome, *viz.* heterochromia iridum, white forelock, and congenital deafness. The distribution in fact seems to be quite random with respect to all of these factors. A simultaneous analysis would be difficult owing to the marked irregularities to be expected in small human families. In attempting an analysis of each factor separately, I shall make use of the method of "expected subclass frequencies" (Snedecor, 1934) as a means of controlling the disproportionality in subclass numbers. Also, in the analysis by sexes and sibships the fact that 3 degrees of freedom have been used up in maximizing the difference between the two phenotypes W and N will be ignored, as though the function L had been derived from a wholly different set of data. This should have the effect of exaggerating the apparent significance of the sex and sibship variations and their interactions with the phenotype difference; even so, these differences will appear to be non-significant.

Variations by sibships. Confining the analysis to the 15 sibships in fig. 2 which contain at least 1 member of W and 1 of N, and using the method of expected subclass frequencies, the variation in L may be analyzed in the following manner:

Variation in L	*D.F.*	*Sum of Squares*	*Variance*
Between phenotypes (W *vs.* N)	1	1675.17	
Between sibships	14	38.01	2.71
Phenotype-sibship interaction	14	39.61	2.83
Between sibs of same phenotype	33	192.88	5.84

With respect to the average value of L and the difference between the two phenotypes, the sibships are more homogeneous than one would expect on an average, and there is thus no evidence of significant modifying genetic factors.

Sex. Although one might expect males to have somewhat larger interocular dimensions than females, the differences are negligible in the sample of 70, both among members of W and among members of N (table 1). Furthermore, the age distribution in the two sexes is very similar (fig. 2). Consequently the data for the two sexes were combined in constructing the function L. It remains to be seen that with respect to the resulting L there is no significant difference between the sexes (both phenotypes combined), and no significant difference between the phenotype difference (W − N) in the two sexes (i.e. sex-phenotype interaction):

Variation in L	*D.F.*	*Sum of Squares*	*Variance*
Between phenotypes (W *vs.* N)	1	1799.84	
Between sexes	1	9.60	9.60
Sex-phenotype interaction	1	1.94	1.94
Within sex-phenotype classes	66	453.82	6.88

Age. The question might be raised as to whether d.c.m.l. is something which becomes more or less pronounced with advancing age. Gauged by the function L there is clearly no suggestion of this from figure 2. One would also guess that if age were taken into account as a fourth variable it would be found to contribute nothing to the discrimination of the two phenotypes over and above what is accomplished by the three measurements a, b and c. No analysis of this problem has been attempted, however.

Associated anomalies. Concerning the question of association or "correlation" between the several anomalies, two different issues must be distinguished. There is first the question whether these anomalies are correlated in the population as a whole, and whether the concept of a syndrome is justified in that sense; for example, we may ask whether heterochromia occurs more fre-

quently in individuals having d.c.m.l. than it does in the general population, and similarly for the other combinations. These associations seem rather clearly established from Waardenburg's study, but I shall not be concerned with the lines of evidence on such matters. Accepting the existence of the syndrome and the genetic conclusion that it is caused by a dominant "gene" having several "different" manifestations, there arises the question whether these manifestations are independent of one another *within* the syndrome. In other words, although Dr. Waardenburg has estimated the penetrances for the various anomalies, we may ask further whether these probabilities can be assumed to apply independently in individuals having the genetic factor for the syndrome

TABLE 2. COMPARISON OF EIGHT H-A-D CLASSES AMONG 63 INDIVIDUALS POSSESSING THE SYNDROME

STATISTIC	O	H	A	D	HA	HD	AD	HAD	TOTAL
Number, X	25	8	4	8	5	6	4	3	63
Exp. No., m	20.392	10.942	6.942	10.196	3.725	5.471	3.471	1.862	63.000
$(X-m)^2/m$	1.041	0.791	1.247	0.473	0.436	0.051	0.081	0.696	$4.816 = \chi^2$
Sum L, $S(L)$	158.88	46.80	15.26	50.99	27.06	30.69	24.28	16.11	370.07
Mean L, $\bar{l}$	6.355	5.850	3.815	6.374	5.412	5.115	6.070	5.370	5.874
Exp. Sum, $m\bar{l}$	129.02	64.01	26.48	64.41	20.16	27.98	21.07	10.00	363.13
H k_1	22	−41	22	22	−41	−41	22	−41	
A k_2	16	16	−47	16	−47	16	−47	−47	
D k_3	21	21	21	−42	21	−42	−42	−42	
H × A k_4	352	−656	−1034	352	1927	−656	−1034	1927	
H × D k_5	462	−861	462	−924	−861	1722	−924	1722	
A × D k_6	336	336	−987	−672	−987	−672	1974	1974	
H × A × D k_7	7392	−13776	−21714	−14784	40467	27552	43428	−80934	

as a whole, or whether, on the other hand, there exists some kind of "ordering" of the several effects.

I shall restrict the analysis here to four of the anomalies described, *viz.* heterochromia iridum (H), white forelock or circumscribed albinism of the head hair (A), congenital deafness (D), and the eyelid anomaly d.c.m.l., the latter being now measured by the function L. We may represent the 8 combinations of the first three traits by O, H, A, D, HA, HD, AD, HAD, the letter O standing for the absence of all three. All of these combinations occur among the measured individuals in Waardenburg's families, with frequencies (X) as shown in the first row of table 2. The total (63) consists of all measured cases of d.c.m.l. (positive L-value) and this therefore includes all cases of the syndrome W with the exception of the two probands 4 and 8. In addition

to the 43 remaining cases of d.c.m.l. represented in fig. 2, there are 20 cases previously not used because of the incomplete recording of their sibships.

In estimating the penetrances for H, A and D, Dr. Waardenburg excluded probands since these were selected initially for the presence of deafness (D) as well as d.c.m.l. Here no such refinement of the sample seems necessary, as we are concerned only with the observed *associations* of the 3 traits. Letting H, A and D stand for the observed proportions of each trait among the total of 63 cases, we find $H = (8 + 5 + 6 + 3)/63 = 22/63$, and similarly $A = 16/63$, and $D = 21/63$. On the hypothesis that the three manifestations are independent in members of W, we may now calculate the expected frequencies (m) in the 8 classes:

$$m_{\text{O}} = 63(1 - H)(1 - A)(1 - D) = 20.392,$$
$$m_{\text{H}} = 63H(1 - A)(1 - D) = 10.942,$$

and similarly for the other classes, as shown in the second row of table 2. Comparing these with the observed numbers, we have $\chi^2 = 4.816$. Although there are 8 classes, only 4 degrees of freedom remain in consequence of using the observed proportions H, A and D and the total (63) in computing the expectations. Using the orthogonal polynomial coefficients (k) tabulated in the last 7 rows of table 2, we may calculate seven chi-squares,

$$\chi_i^2 = \frac{S^2(k_i X)}{S(k_i^2 m)}, \; i = 1, 2, \cdots 7,$$

but the first three are dummy comparisons ($\chi^2 = 0$); the last four furnish us with the desired analysis:

	D.F.	*Chi-square*
H × A association	1	2.146
H × D association	1	0.873
A × D association	1	1.047
H × A × D interaction	1	0.749
	4	4.815

The largest deviation consists in a positive association between the two pigmentary anomalies H and A, but none of the chi-squares is significant.

Now since the eyelid anomaly seems to be a kind of "key" abnormality in the syndrome, occurring in almost all individuals who can be assumed to be carriers of the genetic factor, it might be thought that its "severity" or degree of development, as measured by the function L, would perhaps be found to be related to the presence or absence of the other anomalies. For example, we might ask whether individuals having a more pronounced dystopia of the inner canthi, among the various members of a family so affected, are more apt

to display deafness, or whether perhaps the reverse is true, and similarly for the other anomalies. Figures 2 and 3, as we have seen, suggest no such trends. To investigate the matter systematically we may analyze the 7 independent deviations among the means ($\bar{l}$) in the 8 H-A-D classes in factorial fashion. We have just seen that there is little disproportionality among the observed numbers (X) in these classes. However, replacement of these by the expected numbers (m) restores the additive property to the sums of squares, and we then compute seven such sums of squares,

$$S_i = \frac{S^2(k_i m\bar{l})}{S(k_i^2 m)}, \; i = 1, 2, \cdots 7,$$

using the same coefficients (k_i) and divisors $S(k_i^2 m)$ employed in the above analysis of chi-square. This leads to the following analysis of variance:

Variation in L	*D.F.*	*Sum of Squares*	*Variance*
Between 8 H-A-D classes			
H+ (heterochromia iridum) *vs.* H−	1	1.515	1.515
A+ (white forelock) *vs.* A−	1	17.647	17.647
D+ (deafness) *vs.* D−	1	0.417	0.417
H × A interaction	1	6.521	6.521
H × D interaction	1	4.030	4.030
A × D interaction	1	7.815	7.815
H × A × D interaction	1	1.491	1.491
Within H-A-D classes	55	285.210	5.186

In conclusion, although dystopia canthorum and the other anomalies described by Waardenburg seem to constitute a well demarcated genetic complex, there appears to be a statistical independence between the several manifestations in individuals possessing the genetic factor. This conclusion is, of course, a tentative one; the method of analysis used may be questioned and, in any case, is susceptible of a variety of modifications. Also, it is possible that a different conclusion might emerge if the several families were reclassified, making use of those traits which, as noted by Dr. Waardenburg, may possibly be equivalents of heterochromia and white forelock.

The general problem is one which deserves investigation for many interesting hereditary syndromes in man. If the several features in any syndrome were found to be "patterned" in their appearance, such information could have practical value in medical prognosis, especially in those cases where the abnormalities appear late in life. Also, the patterning in itself might suggest physiological or embryological interpretations which could then in some cases be subjected to further study by clinical or laboratory means. Finally, the presence or absence of phenotypic correlations within syndromes could conceivably have some significance in terms of the ultimate genetic units responsi-

ble for such complexes. If, for example, it were known to be generally true that genes located close together in a chromosome have no greater likelihood of phenotypic interaction than those located far apart, then an absence of intra-syndrome correlations could perhaps be regarded as a clue that linked genes were involved. At present it seems doubtful whether any such principle can be applied. In any case, we shall never be in a position to answer this and other related matters unless the phenotypic interrelations within syndromes are systematically looked for.

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A Genetic and Statistical Study of Psoriasis

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INTRODUCTION

Two excellent reviews of the literature on psoriasis have been published in recent years, the first by Lerner in 1940 and the second by Romanus in 1945. We shall, therefore, content ourselves with a discussion of the two most extensive statistical investigations of which we are aware, namely those of Hoede (1931) and Romanus (1945).

Hoede (1931) studied the records of 1,437 psoriatic patients seen by various physicians over a period of fifty years. Included among these were 539 patients seen by him in the five years previous to the publication of his paper and from whom he obtained detailed pedigrees. His genetic analysis is based on these pedigrees. His conclusions may be summarized as follows: Among the probands (index cases) males were more frequent than females (828:609); the frequency of the age at onset rises until 20 years and then falls off sharply, onset being earlier in females than in males (based on 959 cases); the proportion of diseased sibs is 4.48 per cent when both parents are healthy and 10.67 per cent when one parent is psoriatic; in families with male probands more male relatives than female relatives are affected with psoriasis, while in families with female probands more females than males are affected (the parents, sibs and children were treated separately; all others were grouped); these differences, while statistically insignificant, are always in the same direction; there is no significant association between the sex of a psoriatic parent and the sex of the proband. Finally, Hoede concluded that "psoriasis is an irregular dominant, which is incompletely sex-limited."

Romanus' (1945) material was composed of patients examined prior to 1922, in either of two hospitals in Stockholm. His follow-up study was begun in 1943: hence a patient to be included in this study had to have been examined at least 21 years prior to the commencement of the follow-up study and had to have survived until the follow-up study was begun. Consequently, of 1,417 patients whose records were examined only 768 (54%) were followed, 438 (31%) were dead, and 211 (15%) could not be traced. The follow-up examination and interview were thoroughly and carefully done. Romanus' conclusions may be summarized as follows: Among the original 1,417 probands, males were more frequent than females (943:474); this was also true among the patients followed, although to a lesser extent than in the larger original group (461:307); in the follow-up group one-half the males were affected before 19 years of age and three-fourths before 26 years, while one-half the females were affected before 12 years of age and three-fourths before 19 years (these values will be

discussed later). Romanus did not separate the probands and their families into groups depending on whether the parents were psoriatic or not, and in computing the frequency of psoriasis among the patients' sibs and children he used only those who were more than 30 years of age. Romanus reported the frequency of psoriasis among the patients' parents to be 8.3 per cent, among sibs 9.0 per cent, and among children 13.0 per cent; he found no evidence of a significant association between the sex of the patient and that of an affected parent or sib. Finally, he concluded that his data indicated "a dominant heredity with a manifestation probability (that is penetrance) of about 18 per cent."

The conclusions of these two workers will be examined in greater detail in a later section of this paper.

It should be stated that with very few exceptions workers in the field seem agreed that a predisposition to psoriasis is inherited via a dominant gene with reduced penetrance. Nevertheless a careful reading of the literature indicates that this hypothesis is based on biased or incompletely analyzed material and that the foregoing hypothesis does not account for such known facts as the increased frequency of psoriasis among the sibs of patients who have a psoriatic parent. We therefore decided to undertake the present investigation, hoping to be able to furnish a clearer picture of the situation than that which exists at present.

THE MATERIAL

The material on which this study is based consists of information concerning parents, sibs, spouses and children obtained from 464 consecutive, and therefore unselected, psoriatic patients examined by members of the Section of Dermatology. The information was collected on a special form, and particular pains were taken to obtain as accurate reports from the patients as possible. Nevertheless, the data undoubtedly contain uncertainties and errors with respect to the ages and to the presence or absence of psoriasis among the patients' relatives. We have exercised every effort to keep these errors to a minimum and know of no way of reducing them further short of interviewing and examining all of the individuals mentioned on the forms. This was not possible for two reasons: (*a*) the relatives were distributed all over the world, and (*b*) many of them were already dead. Although it seems probable that the frequency of psoriasis reported by the patients for relatives is too low, we believe that the errors of reporting made by the patients were of such a nature as not to affect materially any of the conclusions which will be drawn from the study.

Blood uric acid levels were determined for 177 patients and for the available immediate relatives of another 5 patients.[1] The details of this aspect of the study will be reported elsewhere; only the conclusion pertinent to this report will be referred to in this paper.

[1] We wish to express our gratitude to Dr. M. H. Power of the Division of Biochemistry for these determinations.

THE DATA

Age at Onset. The age at onset is that reported by the patient and is subject to many inaccuracies. Some patients came to the Mayo Clinic for reasons other than psoriasis and were unaware of the fact that they had psoriasis, in which event the age of onset is recorded as the age at which, according to the patient's statement, the lesion appeared. In other instances the patient was aware of his psoriasis and reported an age of onset. In some cases this was the age at diagnosis and in others it was the age at which the patient recalled the presence of the first eruption. An additional source of inaccuracy is introduced by the all-too-human characteristic of vagueness about dates. These uncertainties in our data are characteristic of all studies of this type. Hence, while it is possible to compare the results of various studies with each other, it is quite impossible to provide an accurate distribution of age of onset.

TABLE 1. DISTRIBUTION OF THE PROBANDS ACCORDING TO THE REPORTED AGE AT ONSET OF PSORIASIS

AGE, YEARS	TOTAL		MALES		FEMALES	
	Number	Per cent	Number	Per cent	Number	Per cent
0–9	43	9.3	14	5.6	29	13.6
10–19	104	22.5	47	18.7	57	26.8
20–29	100	21.6	62	24.7	38	17.8
30–39	93	20.0	57	22.7	36	16.9
40–49	59	12.7	36	14.3	23	10.8
50–59	48	10.3	24	9.6	24	11.3
60–69	15	3.2	10	4.0	5	2.3
70–79	2	0.4	1	0.4	1	0.5
Total.....	464	100.0	251	100.0	213	100.0

The distribution of the probands at the reported age of onset is shown in table 1. The modal age at onset in females occurs during the age interval 10–19 years and in males during the age period 20–29 years, the average ages of onset being 28 and 32 years, respectively.

Fifty-eight of the patients' sibs were reported to be psoriatic, and for 45 of these the age at onset was reported. The data (table 2) were examined for possible association between the age of onset in the patient and in his affected sib. While the data are few it is clear that they do not indicate any association between the ages of onset of the patient and his affected sib.

The age of onset was reported for only 31 of the 55 affected parents. The data are therefore too few to yield satisfactory information concerning a possible association between the age of onset in the patient and in his affected parent; however, they are presented in table 3 to make them available to supplement other data which may be collected in the future. More data would be necessary before the validity of the apparent correlation between the ages of onset in the

patient and the affected parent could be tested as was done in the case of diabetes by Harris (1950) and by Steinberg and Wilder (1950).

Sex Ratios. Reference to table 1 will show that 251 (54.1%)of the 464 probands were males. The excess of males in our sample is not statistically significant ($P \leqq 0.08$). However, the fact that the sample is relatively small, plus the fact that an excess of males (in some cases a significant excess) has been

TABLE 2. DISTRIBUTION OF PSORIATIC SIBS ACCORDING TO THEIR AGE AT ONSET AND THAT OF THE RELATED PATIENT

AGE OF PATIENT AT ONSET, YEARS	AGE OF SIBS AT ONSET, YEARS							TOTAL	MEAN AGE OF SIBS AT ONSET, YEARS
	0–9	10–19	20–29	30–39	40–49	50–59	60–69		
0–9	—	2	1	1	1	—	—	5	25
10–19	1	6	3	1	3	—	—	14	23
20–29	—	7	3	—	1	2	1	14	29
30–39	—	1	2	4	—	1	—	8	30
40–49	—	—	—	1	—	—	1	2	50
50–59	—	—	1	1	—	—	—	2	28
Total....	1	16	10	8	5	3	2	45	

TABLE 3. DISTRIBUTION OF PSORIATIC PARENTS ACCORDING TO THEIR AGE AT ONSET AND THAT OF THE RELATED PATIENT

AGE OF PATIENT AT ONSET, YEARS	AGE OF PARENTS AT ONSET, YEARS								
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Unknown
0–9	—	3	—	1	—	—	—	—	2
10–19	1	—	3	4	2	2	—	—	11
20–29	—	1	—	1	2	—	—	2	4
30–39	—	—	1	—	2	—	1	1	4
40–49	—	—	—	—	—	1	—	2	2
50–59	—	—	—	—	—	—	—	1	1
Total....	1	4	4	6	6	3	1	6	24
Mean age of patients, years.....	15	10	20	15	25	25	35	38	23

reported in almost all previous investigations (see Romanus, 1945, for a review of the literature), requires that a further examination of the data concerning the possible explanation of this excess be undertaken.

The 464 probands had 1,830 sibs. The sex was reported for 1,791 of them; of these 943 (52.6%) were males; the excess over 50 per cent is here significant ($P < 0.05$). A chi-square comparison of the sex ratio among the patients with that found among their sibs showed that a difference as great as or greater than

the one found would be expected to arise by chance in slightly more than 50 per cent of such comparisons. On the basis of this comparison there is no reason to assume a greater frequency of males among psoriatic patients than among their sibs. From this it follows that there is reason to question the biologic significance of the observed excess of males among psoriatic patients.

A further test may be obtained by comparing the frequency of psoriasis among all males in the study (patients and their sibs) with that found among all the females. These frequencies are 24.0 per cent (287/1,194) and 21.9 per cent (232/1,061) respectively. A chi-square test shows that at least as great a difference would occur by chance in about 20 per cent of such comparisons. Here again the analysis indicates that the observed excess of males among psoriatics is probably not of biologic significance. The analysis raises the question whether families of psoriatics tend to have more males in them than do families in general. Discussion of this question will have to be postponed until the data necessary for its analysis are available.

TABLE 4. RELATION BETWEEN THE SEX OF PATIENTS AND THAT OF THEIR AFFECTED PARENTS AND SIBS

PATIENTS	AFFECTED PARENTS		AFFECTED SIBS	
	Male	Female	Male	Female
Male	16	15	23	8
Female	13	11	13	11
Total	29	26	36	19

Table 4 shows the data concerning the relation between the sex of the patient and that of his affected parent (none of the patients reported both parents psoriatic) and sibs (3 sibs whose sex was not reported are not included in the table). Note that the male relative is the more frequently affected regardless of the sex of the patient. The differences, however, are not statistically significant.

Birth Order. Table 5 shows the distribution of the probands according to their order of birth. For obvious reasons the 25 one-child sibships are not included in the table. The rightmost column of the table shows the number of probands expected in each position if no relation between order of birth and susceptibility to psoriasis is assumed. The last row shows the number expected in the entire sample in each birth position. These figures are derived by summing the appropriate figures of the rightmost column. Thus for the first and second birth orders all the values in the rightmost column were totaled; for the order 3 all except the expected values for two-sib families were totaled; for order 4 all except the expected values for two-sib and three-sib families were totaled, and so on. The row above the last row shows the number observed in each birth

order. The deviations are clearly small. A chi-square test based on a 2 by 10 table (the values for birth orders 10–13 were combined) gave a chi-square value of 4.894 with 9 degrees of freedom, and $P > 0.80$.

Hyperuricemia and Psoriasis. Lobitz and Brunsting (unpublished data quoted in Ormsby and Montgomery [1948] and personal communication) found an increase in the concentration of uric acid in the serum of a high percentage of patients hospitalized for psoriasis. As a follow-up of this study the serum uric acid levels were determined for 177 patients (102 males, 75 females). Concentrations less than 6 mg. per 100 cc. of serum in the male and 5 mg. per 100 cc.

TABLE 5. BIRTH ORDER OF PATIENTS

SIZE OF FAMILY	BIRTH ORDER													TOTAL	NUMBER EXPECTED IN EACH BIRTH POSITION
	1	2	3	4	5	6	7	8	9	10	11	12	13		
2	29	31	—	—	—	—	—	—	—	—	—	—	—	60	30.0
3	32	31	21	—	—	—	—	—	—	—	—	—	—	84	28.0
4	17	20	18	14	—	—	—	—	—	—	—	—	—	69	17.2
5	10	6	17	14	18	—	—	—	—	—	—	—	—	65	13.0
6	4	5	13	7	5	6	—	—	—	—	—	—	—	40	6.7
7	2	9	4	6	3	10	2	—	—	—	—	—	—	36	5.1
8	3	3	6	2	1	6	4	1	—	—	—	—	—	26	3.2
9	3	1	2	7	4	1	4	1	1	—	—	—	—	26	2.9
10	3	1	4	0	1	0	1	2	2	2	—	—	—	16	1.6
11	0	0	0	1	2	0	2	0	1	1	1	—	—	8	0.7
12	0	0	0	0	0	0	1	0	1	0	0	1	—	3	0.3
13	1	0	0	1	0	1	1	0	1	0	1	0	0	6	0.5
Total observed	104	107	85	52	34	26	15	4	6	3	2	1	0	439	
Total expected	109.2	109.2	79.2	51.2	34.0	21.0	14.3	9.2	6.0	3.1	1.5	0.8	0.5	439.2	

of serum in the female were considered normal. Four male and 6 female patients were less than 20 years of age and were not included in this portion of the analysis because it has been shown that uric acid concentrations are not elevated in young persons possessing the genetic factor for gouty hyperuricemia (Smyth *et al.*, 1948). Among the males 48 per cent (47/98) and among the females 27 per cent (19/69) showed hyperuricemia. The data thus confirm Lobitz and Brunsting's findings.

Both parents of each of 4 unrelated patients were tested for hyperuricemia. All 8 parents had levels of uric acid well within the normal range of values. It thus appears that the relation between hyperuricemia and psoriasis is not the same as that between hyperuricemia and gout, where it has been shown that hyperuricemia is present in at least one of a gouty patient's parents and where it

has been shown also that hyperuricemia may be present prior to the development of clinical symptoms of gout (Smyth *et al.*, 1948; Stecher *et al.*, 1949).

Genetic Analysis. It has been shown in a previous section of this paper that there is no association between the sex of the proband and that of his affected parent or sib; hence for the discussion which follows we may ignore the sex of the individuals concerned. The sibship size and the number of affected individuals are presented in table 6 for those patients neither of whose parents were psoriatic and for those with one parent psoriatic. No patient reported both parents psoriatic. It is clear from the table that there is no tendency for a disproportionate number of the affected sibs to come from one or two families.

TABLE 6. SIZE OF FAMILY AND NUMBER AFFECTED, INCLUDING PATIENT

SIZE OF FAMILY	NUMBER AFFECTED						
	Neither parent psoriatic				One parent psoriatic		
	1	2	3	4	1	2	3
1	22	—	—	—	3	—	—
2	45	5	—	—	6	4	—
3	67	5	—	—	11	—	1
4	55	6	—	—	6	2	—
5	59	3	—	—	3	—	—
6	32	5	—	—	3	—	—
7	26	2	—	—	3	4	1
8	22	1	1	—	2	—	—
9	22	2	—	—	1	—	1
10	11	1	1	—	2	—	1
11	5	2	—	—	1	—	—
12	2	1	—	—	—	—	—
13	5	0	—	1	—	—	—
Total.....	373	33	2	1	41	10	4

No sibship had more than 4 affected members including the proband, and the one sibship with 4 affected contained a total of 13 children. Six sibships had 3 affected members each. These sibships consisted of one each with 3, 7, 8 and 9 members, and two with 10 members.

When neither of the patient's parents was psoriatic 2.45 per cent (40/1,630) of the sibs were psoriatic, while when one parent was psoriatic 9.00 per cent (18/200) were psoriatic. As mentioned previously, 55 (5.9%) of the patients' parents were psoriatic.

In our sample psoriasis occurs among the patients' sibs almost four (3.7) times as frequently when one parent is psoriatic as when neither parent is psoriatic, while in Hoede's sample the corresponding ratio is almost 2.5. While it cannot be said with certainty at this time what the increase in frequency is

when one parent is psoriatic, it can be stated that a marked increase does occur and that it is probably more than double. Although these data confirm the presence of an hereditary component in the causation of psoriasis they contradict the conclusion advanced by Hoede, Lerner, Romanus and others that this component is inherited as an irregular dominant—that is, as a dominant with incomplete penetrance. Such an hereditary pattern requires that the frequency of psoriasis among the patients' sibs be independent of the presence or absence of psoriasis in a parent.

What then is a likely genetic explanation of these data? We wish to state at once that a satisfactory answer cannot be given at this time. However, certain possibilities can be ruled out and we should like to consider them. Any hypothesis of sex-linked inheritance, either partial or complete, is incompatible with the data because of the independence of the sex of the patient and that of the affected parent and of the affected sibs; secondly, no single-gene hypothesis,

TABLE 7. FREQUENCY OF NON-CONSANGUINEOUS AND OF CONSANGUINEOUS MARRIAGES AMONG PARENTS OF PSORIATIC PATIENTS

TYPE OF MATING	NUMBER OF MARRIAGES		
	Non-consanguineous	Consanguineous	No information
One parent psoriatic	52	1*	2
Neither parent psoriatic	389	3†	17

* First cousins.

† One marriage of first cousins; one of cousins, degree not stated; one of uncle and niece.

dominant or recessive, with or without complete penetrance, can explain the present set of data, although a single *recessive* gene with incomplete penetrance could possibly explain Hoede's data. We are forced to assume more than a single gene to explain the observations.

One possibility is that the clinically observed group of psoriatic patients is genetically heterogeneous and that different loci are involved as units—one or more dominant and one or more recessive. In this case it would be reasonable to assume that the patients with non-psoriatic parents are predominantly homozygous recessive, while those with a psoriatic parent are heterozygous for a dominant gene. We should expect, therefore, in a sufficiently large sample, to find a greater (though perhaps not much greater) frequency of consanguinity among the parents of the former group of patients than among the parents of the latter group. Our sample is too small to enable us to test this point adequately, but the data—which, incidentally, lend no support to this view—are recorded in table 7 for future use.

On this same assumption we should expect also to find a greater frequency of psoriasis among the children of the patients who have a psoriatic parent than among those with healthy parents. We should like to point out that the fre-

quencies to be presented are low because the average age of the patients' children is low. It is not necessary for the present purposes to make corrections for this because the point at issue is not the absolute frequencies but the relative frequency of the disease among the children of patients with neither parent psoriatic as compared to that observed among the children of patients with one psoriatic parent. The frequency of psoriasis among the former group of children is 2.5 per cent (16/637) and among the latter 1.7 per cent (1/59). The figures are clearly not in accord with the prediction but there are too few offspring from patients with a psoriatic parent to establish the point with statistical certainty.

TABLE 8. CALCULATION OF THE NUMBER OF POTENTIAL PSORIATICS AND THE PERCENTAGE RECOGNIZED AS FRANK PSORIATICS

AGE, YEARS	1 PERCENTAGE OF THOSE STARTING A GIVEN DECADE WHO SURVIVE IT*	2 PERCENTAGE OF PATIENTS OCCURRING IN EACH DECADE OF AGE	3 RELATIVE NUMBER OF POTENTIAL PSORIATICS	4=2+3 TOTAL OF POTENTIAL AND FRANK PSORIATICS	5=2/4 PERCENTAGE IDENTIFIABLE
0-9	96.2	9.3	99.1	108.4	8.6
10-19	99.2	22.5	75.8	98.3	22.9
20-29	98.6	21.6	53.1	74.7	28.9
30-39	97.8	20.0	31.9	51.9	38.5
40-49	94.9	12.7	17.6	30.3	41.9
50-59	88.4	10.3	5.3	15.6	66.0
60-69	75.1	3.2	0.8	4.0	80.0
70-79	51.4	0.4	0.0	0.4	100.0

* Estimated for United States white population, July 1, 1948.

It has been noted that in the present sample psoriasis occurs among the patients' sibs with a frequency of 9.00 per cent when one parent is affected and with a frequency of 2.45 per cent when neither parent is affected. Because of the variability of the age of onset of psoriasis the frequencies observed are lower than they would be if all the individuals in the sample had reached, say, 70 years of age. Approximate corrections can be made for the fact that the ages of the individuals in the sample vary from the first through the ninth decade. A very useful method has been developed by Pincus and White (1933). It is based on the reasonable assumptions that the survival rate of those not frankly afflicted with the disease under review but genetically liable to it is not different from that of the general population and that the distribution of the age of onset derived from the present sample is representative of the age of onset in the patients' sibs.

The details of the procedure may be explained with the aid of tables 8 and 9. Column 1 of table 8 shows the percentage surviving each decade of life (based on life tables of the estimated United States white population as of July 1, 1941, published in *Vital Statistics of the United States*, 1948), and column

2 shows the percentage of the probands which became psoriatic in the indicated decade. The 0.4 per cent of the patients who became ill during the eighth decade of life represent 51.4 per cent (column 1, table 8) of those who were potential psoriatics in the seventh decade. This equals a relative total of 0.8 in the seventh decade who were potential but not actual psoriatics. This figure is entered in column 3 and added to the 3.2 who were actual psoriatics in the seventh decade to give the value 4.0 entered in column 4. These equal 75.1 per cent of the total who were potential psoriatics in the sixth decade. The corrected value, 5.3, is entered in column 3. The procedure outlined is repeated until columns 3 and 4 are completed. It is now possible to compute the proportion of actual psor-

TABLE 9. MEAN PROPORTION OF POTENTIAL PSORIATICS DETECTED AMONG THE PATIENTS' SIBS IN THE PRESENT SAMPLE

AGE, YEARS	NEITHER PARENT PSORIATIC			ONE PARENT PSORIATIC		
	1	2	3	1	2	3
	Percentage of sibs of this age	Percentage identifiable	Relative number in percentage which would be detected	Percentage of sibs of this age	Percentage identifiable	Relative number in percentage which would be detected
0–9	4.6	8.6	0.4	8.3	8.6	0.7
10–19	5.5	22.9	1.3	16.6	22.9	3.8
20–29	12.3	28.9	3.6	13.5	28.9	3.9
30–39	18.3	38.5	7.0	18.6	38.5	7.2
40–49	22.6	41.9	9.5	19.2	41.9	8.0
50–59	20.8	66.0	13.7	16.1	66.0	10.6
60–69	12.0	80.0	9.6	6.2	80.0	5.0
70–79	3.5	100.0	3.5	1.0	100.0	1.0
80–89	0.4	100.0	0.4	0.5	100.0	0.5
Total.....			49.0			40.7

iatics realized at each decade from among the total of all psoriatics (potential as well as actual) present in the decade. This equals the number in column 2 divided by the number in column 4 and multiplied by 100 to give a percentage value. The results are entered in column 5. These values may now be used to compute the proportion of potential psoriatics among the patients' sibs who would be recognized as actual psoriatics. The figures are in table 9. The values in column 1 show the age distribution of the patients' sibs; the age of the sibs who were psoriatic was taken as that at which the onset of psoriasis occurred. Column 2 reproduces the figures of column 5 of table 8. Column 3 of table 9 is derived by multiplying column 1 by column 2 and dividing by 100, and shows the proportion of all potential psoriatics in this population of sibs that would be recognized in the indicated decade. The total of column 3 equals the total proportion of the potential psoriatics that would be recognized in this popula-

tion. Thus when neither parent is psoriatic 49.0 per cent of the potentially psoriatic sibs of the patient would be recognized as such. The corresponding value when one parent is psoriatic is 40.7 per cent. These figures may be used to correct the observed frequencies of actual psoriatic patients, namely, 2.45 and 9.00 per cent respectively, to obtain the total frequency of potential plus actual psoriatics in the sample. The corrected values are 5.0 and 22.1. It must be emphasized that these corrections are very approximate. They do, however, yield values which do not differ greatly from those which would be obtained if psoriatics were homozygous recessive for two pairs of genes, if it is assumed that among matings which yield psoriatic offspring those matings in which both partners are nonpsoriatic are predominantly between a double homozygote and a double heterozygote. Thus when both parents are normal the mating is $AaBb \times AaBb$, which would yield 6.25 per cent of potential psoriatics (the derived value is 5.0 per cent). When one parent is psoriatic the mating would be $aabb \times AaBb$, which would yield 25.0 per cent of potential psoriatics (the derived value is 22.1 per cent). We do not wish to imply that this hypothesis is the correct explanation of the data; we offer it merely as a *possible* explanation and use it to help emphasize that a single-gene hypothesis cannot explain the observations.

DISCUSSION

Age at Onset. The modal and the average ages of onset for the patients reported in the present study are in agreement with those published by previous investigators (Steinke, 1935; Romanus, 1945; and others—see Romanus for review) in that they show an earlier age at onset in females than in males. The values obtained (modes in the age interval 10–19 in females and 20–29 in males; mean ages of 28 and 32 years, respectively) are in agreement with Steinke's but differ considerably from the average ages at onset reported by Romanus, namely, 14 and 18 years in females and males, respectively. This difference is due to the manner in which Romanus selected his probands. As mentioned in a previous section, each patient in Romanus' study had to have been examined for psoriasis at least 21 years before Romanus began his study of him. It follows, therefore, that in general those with an older age of onset would be less likely to have survived the necessary twenty-one-year interval, and consequently the observed sample is biased in the direction of having an excess of individuals with early onset of psoriasis.

Sex Ratios. The analysis presented earlier in this paper indicates that the excess of males found among psoriatic patients in this as well as all other sizable studies probably does not indicate an increased susceptibility to psoriasis among males. We suggest that the excess of males found among psoriatics may not result from a greater susceptibility among males but rather from the fact that there are in these families more males available to become affected.

We have already indicated the necessity for investigating the reason for this excess of males among these families. Unfortunately data for such an investigation are not available at present.

Hoede (1931) reported an excess of affected males among the relatives of male patients and an excess of affected females among the relatives of female patients. Sibs, parents and children were tabulated separately, all other relatives were reported in a group. Our data for parents and sibs differ from Hoede's in that more male than female relatives (parents and sibs) were affected regardless of the sex of the patient (table 4). None of the differences found by Hoede or by us are statistically significant. They are mentioned only because of the stress that Hoede placed on them.

Hoede was sufficiently impressed by the fact that in four sets of comparisons (sex of parents, sibs, children, and all other relatives with the sex of the patient) no reversal occurred to lead him to postulate a sex-limited form of inheritance. However, Hoede's numbers are small, two of the comparisons differ by only one individual, and a third shows equality of numbers. Finally Hoede himself pointed out that a bias may arise because female patients are probably better informed about the occurrence of psoriasis among their female relations and male patients about its occurrence among their male relations, particularly among those more distantly related, and in fact the greatest difference reported in his data occurs among the group of more distant relatives.

In the light of the foregoing analysis of the sex ratios and of the relation between the sex of the patients and that of their affected relatives it seems unnecessary to us to assume sex linkage or sex limitation as a factor in the occurrence of psoriasis.

Genetic Analysis. Before entering into a discussion of our data we should like to discuss Hoede's statement that any investigation of the familial incidence of psoriasis which results in an incidence of less than 33 per cent is one in which the material has not been sufficiently studied. We wish to discuss the meaning, or rather the lack of meaning, of the term "familial incidence." The first difficulty that arises with this term is the meaning of "familial." Many investigators use this term to include any blood relation that can be traced. It is in this sense that Hoede used it. Unfortunately these authors generally fail to state how many of the patients' "uncles and his cousins and his aunts" (with apologies to Gilbert and Sullivan) they have traced. Clearly "familial incidence" depends on this point and in this sense, we suppose, Hoede's statement has some merit. But "familial incidence" depends also on family size. For example, if one were unfortunate enough to encounter only one-child families the "familial incidence" in his study—although worked out in greatest detail—would be much lower than that which would be found by an investigation of only ten-child families. This illustration is extreme, of course, but it does make our point. It is worth noting also that the current trend toward

smaller family size will inevitably lead to a reduction in "familial incidence." Obviously a measure as ill-defined and unstable as this should be abandoned. The statistics that should be reported are the frequencies of occurrence of the disease among the patients' parents, sibs (preferably separated into groups based on whether one or both parents are affected), children (again separated into groups based on whether or not the patient's spouse is affected), and other *specified* relatives, if available. Proper attention will, of course, have to be paid to the method of ascertainment and to corrections, where pertinent, for variable age of onset.

Our data confirm the conclusions of previous investigators that there is an important genetic component in the causation of psoriasis. They do not, however, confirm the hypothesis advanced by these workers that this genetic component consists of a dominant gene with incomplete penetrance or, as Hoede claims, a dominant gene with incomplete penetrance and sex-limited expression (see Romanus, 1945, for a detailed review of the literature). We find that the data (ours as well as Hoede's) cannot be explained by assuming a single dominant gene. It is most probable that any correct explanation will require more than one gene locus, and we have tentatively advanced a hypothesis involving two recessive genes because it approximates our data reasonably well.

Hoede, Lerner and others have advanced the argument that recessive heredity cannot be involved in the causation of psoriasis because the frequency of consanguinity among the patients' parents is too low. This argument is invalid because it does not take into account the fact that the expected increase in consanguinity is low when the gene frequency is high. There is no adequate information concerning the frequency of psoriasis in the population; however, an estimate by Gahan (1943) places the frequency at 1 per cent. This of course means a very high gene frequency and consequently only a slight increase in consanguinity would be expected. Another difficulty arises from our lack of knowledge of the frequency of consanguineous marriages in the United States as a whole or in any of the local areas. Data collected by Glass (personal communication) in Baltimore from pregnant women and by Steinberg (unpublished data) in Rochester, Minnesota, from women during the lying-in period indicate the remarkably low frequency of 0.05 per cent in these two widely separated cities. These figures, it must be emphasized, refer to relatively recent marriages and may be considerably lower than would be found for an earlier generation. Nevertheless, they do indicate a much lower frequency than had been supposed by many investigators.

Our discussion of the genetics of psoriasis is limited to the inheritance of a predisposition to the disease. We have not investigated the problem of the variability of the age of onset. It is possible that there is a genetic component involved in the determination of the age of onset. The analysis of this would require not only a large number of pedigrees with affected parents, sibs and chil-

dren (which we do not have) but also painfully careful attention to pertinent common environmental factors among the members of these families and to accuracy in the determination of the ages of onset.

SUMMARY

1. The data concerning 464 consecutive psoriatic patients and the information obtained from them concerning their parents, sibs and children were analyzed statistically and genetically.

2. The modal age at onset among the patients in this study is, in females, 10–19 years; in males, 20–29 years; the mean ages are 28 and 32 years, respectively.

3. The excess of male psoriatics found among the patients is shown to be essentially the same as the excess of males in these families as a whole. It is shown also that the frequency of psoriasis among the males in these 464 families is not significantly greater than that among the females. There is reason, therefore, to question the biologic significance of the excess of males found among psoriatic patients.

4. No relation was found between the sex of the patient and that of his or her affected parent or sib.

5. There is no relation between birth order and the occurrence of psoriasis.

6. Hyperuricemia occurred in 48 per cent of 98 adult psoriatic males tested and in 27 per cent of 69 psoriatic females tested.

7. All of the 8 parents of 4 psoriatic patients whose serum uric acid level was determined had levels well within the normal range.

8. The frequency of psoriasis among the patients' sibs when neither of the patients' parents was psoriatic was 2.45 per cent. It was 9.00 per cent when one parent was psoriatic. No patient reported both parents psoriatic.

9. The frequency of psoriasis among the patients' parents was 5.9 per cent.

10. The data indicate the presence of a hereditary component in the causation of psoriasis. This component is not—as has been postulated by previous workers—a single dominant gene with incomplete penetrance. It is necessary to assume a minimum of two genes to explain the data. A possible, but not necessarily correct, explanation based on two autosomal recessive genes, the double recessive being predisposed to psoriasis, is advanced.

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A Color Vision Anomaly Showing Holandric (Y-linked) Transmission

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ALL previously published pedigrees of red-green color blindness or color deficiency seem to show sex-linkage and appear to be typical recessive, or nearly recessive, traits due to genes carried on the X chromosome. The defect represented in the pedigree to be presented here does not behave in the usual manner but is apparently a case of holandric or Y-borne heredity.

Ichthyosis hystrix gravior, hypertrichosis of the ears, and a type of webbed toes are examples of characters dependent upon genes assumed to be transmitted via the non-homologous part of the Y chromosome. Such holandric genes are assumed to be passed on to future generations solely through the male line from father to son. The females never exhibit an holandric character nor transmit it to their progeny. It is not possible to state whether holandric characters show dominance or recessiveness, due to the lack of any allele corresponding to the gene of interest.

In the pedigree of the family presented in fig. 1, it is reasonable to assume that the color-anomalous condition is transmitted only through the male line. The females neither exhibit nor carry the trait according to this assumption.

Unfortunately, it has not been possible to test the members of the family in a satisfactory manner. Testing this somewhat scattered family with the anomaloscope was out of the question. None of the females were tested in any way. In the pedigree, *II-9*, *II-14* and *III-7* were tested by the pseudo-isochromatic plates of the American Optical Company and found to be color deficient. The individual *III-1* was refused admission to the Army Air Corps, World War II, because of his color-discrimination deficiency. The propositus (R. K. Cambier, *III-4* of the pedigree) was tested at the Ophthalmology Clinic of the University of Minnesota. The yarn test did not reveal positive data but this test is thought to be less critical. The Stilling-Ishihara pseudo-isochromatic plate tests showed a definite color deficiency. Fifteen of 46 items were missed by both eyes.

While the testing of the members of the family was inadequate, the written or verbal statements were very definite. Each person was quite certain as to his or her possession of, or lack of, a color vision anomaly. The correlation between being a male descendant of *I-1* and having the color anomaly had been recognized in the family for many years.

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If the evidence presented by the members of this family is accurate, it is highly unlikely that the heredity of this color vision anomaly is of the usual X-linked type. We have calculated the probability that this pedigree, as shown, represents the X-linked type of heredity and the probability is negligible.[1]

An alternative assumption is that we have a case of the usual X-linked gene for color deficiency having crossed over to the non-pairing part of the Y chromosome due to some special circumstances of an unusual nature. Were this the case we might expect that the normal allele of the color deficiency gene would still prevent expression of the anomalous gene in the new location in males. This alternative explanation also seems to be an unlikely one.

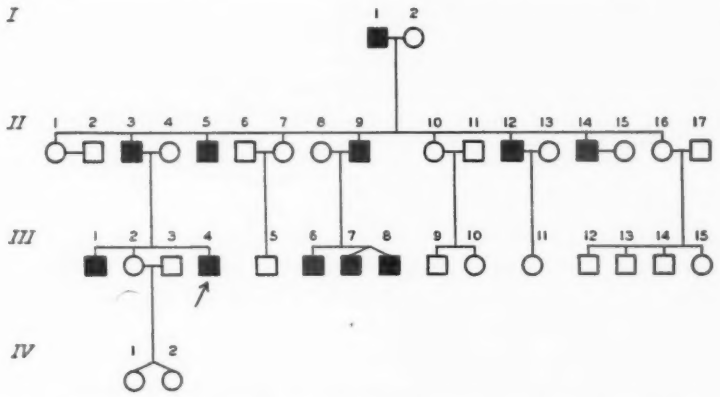

FIG. 1. Pedigree of the Cambier family. The inheritance of the color vision anomaly through the male line is shown by the black squares representing the affected males. The arrow indicates the propositus.

It is most logical to assume that we are concerned with a distinct mutation in the non-homologous part of the Y and that this mutation has no allele on the X chromosome. The Y-borne mutation is therefore an holandric gene with similar effects to the usual X-borne genes but is probably somewhat different in the details of its action.

DISCUSSION

Gates (1946) gives an extensive review of the literature on the inheritance of color-blindness. From his account it seems that there may be two loci on

[1] Given the presence of colorblindness in the propositus and given the sex distribution shown in the pedigree, the probability (P) of finding the reported distribution of color-blind and normal relatives is, on the hypothesis of recessive X-linked inheritance, $P = (\frac{1}{2})^{14}q^2$. Here q stands for the frequency of all X-linked alleles causing color-blindness in males but not in heterozygous females; if we assume $q = 0.1$ then $P = 1/1{,}638{,}000$. (In this calculation it is assumed that *III-7* and *III-8* are dizygotic twins.)

the X chromosome concerned with red-green color-blindness of the usual sort. One locus is concerned with deuteranopia, or green-blindness, and the other with protanopia or red-blindness. Gates also reproduces Cunier's famous pedigree in which color blindness is inherited from mother to daughter only, through five generations. This is a case of hologynic inheritance, the opposite of the holandric type of heredity shown in the Cambier pedigree.

In addition to the two loci for red-green color-blindness on the non-homologous part of the X chromosome and a third locus on the non-homologous part of the Y, shown in the Cambier pedigree, there is a fourth locus concerned with achromatopsia which Haldane (1936) considers to be located in the homologous part of the X and Y chromosomes.

We wonder if it is purely coincidental that all four loci known so far, which are concerned with color vision, are on the sex chromosomes and none on the autosomes. It would seem likely that more than coincidence is involved, though we have no explanation at hand which has experimental evidence to substantiate it.

SUMMARY

A gene causing a deficiency in color vision has been shown to be inherited in the holandric fashion, that is, always through the paternal line. Females could never show this type of color vision deficiency nor carry the gene for it, as the gene seems to be located in the non-pairing section of the Y chromosome.

It is assumed that the gene for color vision deficiency in this family represents a mutation in the non-homologous section of the Y chromosome and that it has no allele in the X chromosome. It has similar effects to those of the usual X-borne genes but probably differs in the details of its action.

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HALDANE, J. B. S. 1936. A search for incomplete sex-linkage in man. *Ann. Eugen.*, Cambr. **7**: 28–57.

BOOK REVIEWS

Studio dei Gemelli

By LUIGI GEDDA (Presso l'Università di Roma, Largo Amba Aradam 1, Roma). Vatican City, (Rome), Italy: Libreria Editrice Vaticana. *Edizioni Orizzonte Medico*. 1951. Pp. 1381, with 548 figures, including 28 in color. 15,000 Lire.

IN JULY of this year the mailman delivered a thick package covered with labels and stamps of the Vatican City. It contained a single volume, almost the size of the directory of the American Medical Association. It was the *Study of Twins* written by Luigi Gedda, chief representative of twin research in Italy, and published in Rome just a few weeks ago.

Gedda's work is a huge collection of data referring to the biology of twins. Though twin research is of a rather recent origin, observations on twinning are many and they accumulate at an amazingly rapid rate. Orientation in the mass of special knowledge has already become very difficult in the field of gemellology. It was high time to synthesize the scattered information, from the literature of the past and present, into a single encyclopedic reference tool.

Studio dei Gemelli is a very imposing work, with its masterly printing and binding. One is reminded of the glorious past of Italian graphic art upon looking at this lavishly illustrated, handsomely ornated volume, a work of art from the 'Città del Vaticano'. The quality of the paper, the typesetting, the numerous photographs and colored folding plates, the red lettering of the cover-title with a pair of playful twins hiding behind it—all contribute to the favorable impression which the book is likely to make even upon those who do not read Italian. Prof. Cesare Frugoni, Director of the Internal Medical Clinic in Rome, justly considers the volume an enrichment of the Italian medical literature, and we may agree with him that it is also a veritable mine of knowledge for international use. Even for Americans, who are notoriously short in language capabilities, the work offers much with its unusual pictorial material and with its lengthy bibliography.

Since it is an Italian publication and the only one of its kind in the modern medical literature a somewhat detailed description of Gedda's work should be of general interest. Being a synthetic reference tool, the book is not to be used for reading in continuity, though its chapters are well written and easy to digest. Its value is not so much in the revelation of new data on twins as rather in the orderly exposition of the known facts.

Of course, what is known and what is not known is entirely individual. The author is not ashamed to confess that his knowledge of twins was very much limited. Indeed, most of us, physicians, know only as much about twinning as our professor of obstetrics tells us during one of his casual lectures. Gedda's interest in 'Nature's experiment' widened when he started his laboratory studies of the redox system of the blood glutathion. That happened more than 10 years ago. Since then he has pursued twins to the outpatient wards, to the clinics and even to the libraries where he found many individual facts on record, facts which were nowhere united, but are now brought together in this 'Collectio Gemellologica'. That Dr. Gedda's interest in the subject became a lasting one is further shown by the establishment of a Twin Study Center at Rome and in the publication of a new journal (*Acta Gemellologica*) to be edited by him. And what, notes Prof. Frugoni, could have been more fitting but that these developments should have occurred in the ancient city of Romulus and Remus!

The general plan of the book is the following. There is a *general part* in 9 chapters (p. 3–403), and a *special part* in six chapters (p. 408–1051). The text is followed by a bibliography of some 7,000 items (p. 1061–1303), an author index (p. 1307–1341), a subject index (1345–1365), and a table of contents (p. 1369–1381). The general part is preceded by a preface, and an introduction (p. xv–xvi). Let me add here as a general remark that it was only in the bibliography and the various indices that I found a few spots on this otherwise splendid work. I shall mention them later.

The chapters of the *General Part* deal with the role of twins in mythology and art (Chap. 1), their place in history and science (Chap. 2), the phenomenon of twinning in plants and animals (Chap. 3), the frequency (Chap. 4), causes (Chap. 5) and genetics of twinning (Chap. 6), embryology (Chap. 7), the peculiarities of plural pregnancy (Chap. 8), and the classification of twins, especially on the basis of isoglutathionemia (Chap. 9).

The chapters of the *Special Part* abound with details on the anatomy (Chap. 10), physiology (Chap. 11), pathology (Chap. 12), normal (Chap. 13) and abnormal psychology (Chap. 14) of twins. There is a final chapter (Chap. 15) in which the methodology of twin studies is described at some length.

It is very hard to give even a superficial narrative account of what the chapters of Gedda's gemellological collection of facts include. The following is a more or less random sampling picked according to subjective taste.

Twinning has interested men of all ages since the time of the Assyr-Babylonian Empire. Semigod twins were adored under many paired names throughout the centuries. Lugalgirra and Meslamtasa, Sin and Nergal, Shamash and Ishtar, Castor and Pollux, Romulus and Remus are among the mythological figures, and they are as well known as the names of Kamala and Amara of modern India.

Twins were celebrated in poems, in dramatic art, in famous fictions and romantic novels. They also became favorite objects of paintings and sculptures as the author's collection of illustrations shows. Shakespeare's *Comedy of Errors* is composed around twins just as is Tristan's *Les Jumeaux de Brigton* in the 20th century. The Milanese surgeon, Andrea Majocchi included in his well-read *Tra Bisturi e Forbici* a romantic episode about the twin sisters Maria and Annina. Ivar and Skul of Undset, Beatrice and Armella of Trilby, Terry and Bianca of Wharton show the general interest of fiction writers in twinning.

Aside from legend and fiction, history also has a row of famous twins (p. 53). Perhaps the oldest pair is Esau and Jacob. Another famous pair is Phares and Zara, the sons of Thamar. The *Noctes Atticae* of Gellius and the *Annals* of Tacitus have also reference to twins. The founder of western monasticism, Saint Benedict, had Sainte Scholastica, for his co-twin sister.

The histories and genealogies of all ages record many twinnings. The rarest case on record seems to be the septuplets in the Römer family in Hameln, Germany, which occurred in 1600 and was perpetuated by a bas-relief. Twins can be found in all countries and at all levels of society, among criminals as well as among the cardinals of the Catholic Church.

Gemellology as a science is of more recent origin. Naturalists and scholars became interested in the ultimate causes of twinning long ago, yet not until Galton's time was the natural phenomenon of plural pregnancy and multiple birth used for general advancement of science. Galton's *History of Twins* was published in 1875. Since then there has been a progressive development of gemellology as the author outlines it in an alphabetical sequence of various countries.

Indeed, twin research in Austria began in 1860, i.e., before Galton. It was initiated by Späth, of Wien. More recent representatives of this branch of science are Bauer (1921)

and Stransky (1937). In France, twin studies were carried out chiefly by psychiatrists, pediatricians (e.g., Apert), and partly by medical geneticists. In 1937 the school of Raymond Turpin established an outpatient ward in the Hôpital St. Louis for the promotion of such studies.

German studies in gemellology were chiefly influenced by the work of Kraus (1919), and of Siemens, the Dutch dermatologist (1921). (*N.B.* Later, during the Hitler regime and World War II many atrocities were committed in a number of internee camps in the name of German gemellological research. C. F. M.)

In Italy the first monograph on twins was published by Chiarugi in 1926. A clinical center for gemellological studies opened in Rome in 1942, owing to the effort of Gedda; it works together with a summer camp at Manziana. There is also an association, established by the twins themselves, for the promotion of twin studies. In Soviet Russia similar studies were formerly under the direction of the Gorky Institute in Moskva. In Sweden gemellological research was initiated by Dahlberg (1926).

In the United States and Canada twin research advanced rapidly. The behaviorist Thorndike had already used twins in 1910 in his psychological studies. Gesell introduced the method known as 'co-twin control'. Newman started his long series of works in twinning in 1917, and wrote his classical study on heredity and environment in 1937. Many other naturalists, physicians, psychiatrists are now actively engaged in gemellological research in this country. There are also other social factors that keep the interest alive on this field, among them the various groups of twins (National Twins Association, 1931; Hollywood Twins Club; Association of Triplets; the Toni Company, etc.)

A large number of publications, special genetic journals and books are now devoted to this branch of human heredo-biology. However, a limitation of twin studies to heredity research would be an incomplete exploitation of Nature's wonderful experimental object. Indeed, twins have been used widely in many sciences since a monozygotic twin offers the most accurate control for every test performed on the co-twin.

Twinning is an universal biological phenomenon (p. 85). It occurs in plants as well as in animals. Single seeds of *Datura stramonium* may produce several adult plants. The Iris may produce 'Siamese' twins. Other plants such as *Gossypium*, *Linum*, and *Triticum* may show similar doubling of the offspring.

In animals the phenomenon of twinning may be natural or artificial. Experimental embryogenesis knows several methods for production of doubling. Certain animals are pluriparous by nature. The origin of plural birth is due either to polyembryony (monozygotism) or to polyovulation (polyzygotism). The conditions have been studied in several invertebrates and vertebrates.

The idea of *parabiosis* of rodents originated in 1861. Bert called this type of postfetal artificial twinning by the name of 'Siamese grafting'. His experiments were repeated by Sauerbruch and Heyde on rabbits, and the life of the grafted pair was called parabiosis in 1908. The research method was further elaborated by Morpurgo.

The study of twinning had great significance for animal breeding. Veterinarians and other practical people have experimented on domestic animals (sheep, cattle), and have published a voluminous literature on the subject.

The statistics of twinning (p. 135) is now very extensive. Gedda's work gives many tables, maps, folding plates which show the frequency of plural birth by various countries and continents. There is an elaborate compilation of quintuplet births, including cases since 1694 (reproduced from MacArthur & Ford). The true incidence of twinning is hard to state since in many multiple pregnancies one (or more) of the twins will die (hidden prenatal

mortality of twins). The old rule of birth ratios has been recently changed from 1:80 to 1:55.5. Others believe, however, that Hellin's rule (1895) still holds good; according to this rule, the birth of an x-geminous product of conception occurs in every 89^{x-1} deliveries.

The frequency of mono- and dizygotism is usually determined by Weinberg's method (1902) though there are also other, more recent, formulas for calculating the qualitative differences. In Italy, monozygotism occurs in 29.2% of all plural births. For triplets the type of zygotism is determined by the Jenkins' formula (1927).

There has been a great deal of speculation on the causes of twinning (p. 179). The older theories took refuge in such factors as atavism, degeneration, intoxication, various maternal peculiarities such as the mother's age, etc. Duncan's law stated that multiparity increases with the age of the mother. Other studies attempted to establish correlation between the type of menstruation, the degree of fertility and multiparity. The author's own observations showed that twins were less frequently born from illegitimate wedlocks (1.01%) than from legitimate marriages (1.20%).

What seems to be certain now is the heredity of a tendency to produce twins. It runs in certain families and in certain races; e.g., Negroes have a high frequency of twin births. Gedda's own statistical studies also justify the theory that the quality of gemination depends upon a hereditary character, the factor G or 'gemellogenetic factor'. Substantiation for this theory is offered subsequently (p. 231) in a chapter which contains pedigrees, an interpretation of the hereditary mechanism of gemination, and the use of twin research as a method for human genetic studies. Mendel's laws, and the research done by Wehefritz is then outlined, with a critical evaluation of methodology.

The book continues with the development of twins (p. 265), their embryonal life, the monstrous duplicities and their probable origin. Even the teratodymus which was mentioned in St. Augustin's *City of God* (Lib. 16, Chap. 8) is recalled by the author. There is a long description of the peculiarities of twin pregnancy, the various forms of mono-, bi- and tri-choriation, the relative prematurity of twins (average 8 to 8½ months), diagnosis, presentation of fetuses, the complications, including abortion, stillbirth, ectopic pregnancy and abnormal forms of delivery.

A separate chapter deals with the phenomenon of isoglutathionemia (p. 375) and the classification of plural births. Much of it is based upon Gedda's own laboratory studies. By synchronous serial determination in the blood and in the tissues (chiefly liver) he found a surprisingly accurate concordance in the glutathion values of co-twins in man and in animals. He talks of *gemellar isoglutathionemia*, and considers it a very characteristic biochemical phenomenon of gemination, a single expression of the general concordance of functional rhythmicity of co-twins. Both mono- and di-zygotic twins may be isorhythmic, or allorhythmic. The state of their biological rhythm, in combination with the type of zygotism, is recommended by Gedda for the classification of twins.

So far the general part of the work!

The special part begins with a collection of anatomical data (p. 407), biometrical measurements, somatic indices, etc., with a cursory run through the various systems of the body, including also data on the distribution of ephelides, on fingerprints, eye region, shape of ear and nose, capillaroscopic observations, and blood groups of twins. The strange 'specularity' (mirror-image symmetry) and the inverted 'laterality' of co-twins has been studied by Gedda for almost eight years (p. 489). The mirror-like correspondence is not only morphological and functional but it is evident also in diseases and in the mental phenomena of twins.

The available physiological data (p. 507) are arranged in the order of the somatic systems (skin, respiratory apparatus, etc.) Postfetal growth and aging is also discussed. The longest chapter (p. 573) is devoted to diseases observed in twins. Of course, these affections are in

general not different from those seen in non-twins. It can be assumed, however, that the usually prematurely-born twins have a certain degree of congenital debility which will probably influence their postnatal life. There are many and diverse diseases which have been described in twins.

The long chapter of pathological cases is followed by a collection of data on the psychological characteristics of twins (p. 839), including the results of mental tests, graphological marks, socio-biographical notes, etc. Experimental psychology is still a relatively new science, and its methods and goals are still indefinite. Nevertheless, it is evident from the existing literature that psychological research gained much by turning its attention to gemination. Studies have been directed in three main channels: 1) comparative examination of the individual psyche of each twin, 2) analysis of the miniature society that exists between the twins from the moment of conception, and 3) utilization of twins as a research method for general psychology.

One of the most interesting sections of Gedda's book is on the psychology of the miniature 'intrageminal society' (p. 907–918). Twins of the uniovular type are in a mysterious correlation, which shows in many ways, occasionally obscuring even the ordinary relations to their families. There is a reciprocal attraction between a pair of monozygotic twins which occasionally may be so strong as to be called a true "elective affinity" (Wahlverwandtschaft) and a 'need of the co-twin'. It may amount to true love ('amor') between the monozygotes who are alter-egoes of one another. Twins of different ova (i.e., dizygotes) do not feel more than a fraternal love to each other.

The psychiatric aspect forms a large and important phase of modern gemellology (p. 929). It started to develop in 1866 when Schutz published cases of twin psychosis and induced psychosis (*folie à deux*). The study of twins was especially useful in understanding the pathogenesis of such diseases as mental deficiency, mongoloid idiocy, dementia praecox, manic-depressive psychosis, involutional and senile psychosis, amentia, alcoholism, the different forms of psychoneurosis and psychopathic personality, including criminal behavior.

The methodology of twin research (p. 995) is discussed in the last chapter of the book. In order to use twins with the greatest efficiency science has worked out certain procedures and rules during the last 50 years; they are critically described in this chapter. They include the collection of clinical material, control and classification of observations (certification of twinning, diagnosis of zygotism by various methods), elaboration and interpretation of material by the comparative method, analysis of correlation, evaluation of heredity and environment, calculus of probability of manifestations, the co-twin control (Gesell, 1927), and the twin family method (Kallmann, 1943).

There is very little in the huge volume to censure or to improve. The few faults I found are in the references and indices. The bibliography (p. 1061–1303) is headlined *General Catalogue of Bibliography on Twins*, and, in a single alphabet of authors, includes over 7,000 references to books and journal articles—more than 300 years of literature (from 1605, the earliest date I saw, to 1948–49). The references are in a dozen or more languages, but titles are mostly translated into Italian from Russian, Japanese, and Hungarian. Some of the references are to little known periodicals. The articles are quoted by indication of journal, volume, paging and year. There are a few unexplained omissions in this order of quotation; here the volume number, there the pagination, and even the title of the paper may be missing.

Some difficulty is caused by the mixture of journal articles with book titles, which could have been avoided by special marks added to book entries. An asterisk (*) before the book title changed my copy of the work into a more useful reference tool. Books are quoted in the accepted manner, yet without the indication of pages, sometimes even without the place

of publication. One finds an occasional book-title with two dates of publication, which gives rise to the reasonable doubt that the dates mean two different editions of the book.

The abbreviations of journal titles are not the internationally accepted standard forms, though they are pretty consistent in shape and use throughout the bibliography. Some of them are hard to identify since an auxiliary list of abbreviated titles is wanting. As mentioned before the bibliography is arranged by the alphabet of authors, but the alphabetization is according to custom of certain European countries which consider O and Ö, also U and Ü, two different letters to be placed at different, subsequent places in the abecedary. Hence, the authors may follow in such order: Schoedel, Schoen, Schokking, . . . Schottky, Schöffel, Schönfeld, Schrank, etc.

One more word on the bibliography! The alphabetical list of twin literature is to be supplemented by some of the references quoted in the main text of the work. But even with such supplemental help the author does not consider his *General Catalogue* exhaustive, and invites readers to help in making the list complete. In following his invitation I call to his attention the printed volumes of the *Index-Catalogue of the Surgeon General's Library*, and the still unprinted Subject File of the same catalog in Washington, D. C. The Index-Catalogue and its files contain many references to twins which are missing from Gedda's list, as I was able to convince myself by a small sampling of the unprinted files.

Most of the omissions seem to be either rare medical dissertations or papers printed before 1900. Out of 24 journal articles, selected at random from the Subject File of the Index-Catalogue, I found only 12 in Gedda's General Catalogue.The missing references were such as the following few:

Abel, W. 1932–33. Physiognomische Studien an Zwillingen. *Zschr. Ethnol.* 64: 379–388.
Jay, R. 1921. **Contribution à l'étude de la grossesse gémellaire.* Paris. 60 pp.
Khaled, M. B. 1939. **Étude du triangle de Scarpa sur coupes microscopiques chez les jumeaux.* Lausanne. 19 pp.
Shapelnikov, G. E. 1913–14. Sluchai rodov dvoinei. *Tr. Imp. Kavkazsk. med. obshch. Tiflis*, 50: 144.
Tissandier, G. 1873–74. Détails sur la mort des frères siamois. *Nature*, Par. 2: 225.
Warren, J. C. 1829. An account of the Siamese twin brothers. *Am. J. Sc.* 17: 212–216.

This does not, however, diminish the great merit of Gedda in establishing a special bibliography of gemellological research, and publishing this list of huge proportions.

There is a triple key to the entire work in form of the indices to a) personal names, b) subject words, and c) the contents. The subject index includes approximately 2,000 subject words such as astigmatism, bronchitis, calligraphy, Caroling dynasty, delirium tremens, monorchidia, etc. From the index the references to the pages are not misleading. In a work of this type it would be desirable in my opinion to have the details of the text more abundantly represented in the subject index. For example, on page 793 there is mentioned a dizygotic female mongoloid pair, one twin showing spastic hypertonic diplegia of the lower extremity, with equinovarus position of the feet. In the subject index this case is represented by two catchwords, both suitable to the case, but neither of them is 'diplegia', or 'spasticità', or 'piede equino-varo'.

On p. 1372 and 1373 the printer became confused putting the contents of chapters 10 and 11 ahead of chapters 8 and 9. Similar printer's errors occur in a few headlines, and in the page numbers listed in the contents.

The author writes in good Italian style which is easy to read. Being essentially a recorder of the research of others, he shows a distinct restraint and critical conservatism in every part of his *Studio*. By offering his gigantic synopsis to the world of science he was able to

show that the phenomenon of twinning is more than just a biological exception or a source of curiosity and humor. Nature's authentic experiment has now become a general method for the study of human biology which needs Gedda's collection as a guide to its better understanding.

CLAUDIUS F. MAYER, *Editor of the Index-Catalogue, Surgeon General's Library, Washington, D.C.*

Blood Groups in Man

By R. R. RACE (Department of Pathology, Cambridge University, Eng.) and RUTH SANGER (Lister Institute, London S.W. 1, Eng.). Oxford: Blackwell Scientific Publications, 1950. Pp. 299. Cloth-bound, £1-10—

DURING the past decade, following the discovery of the rhesus factors and their clinical applications, there have been tremendous advances in the field of blood grouping. In addition to the three systems known before 1940, namely, A-B-O, M-N, and P, five additional independent systems of blood factors are now known, namely, Rh-Hr, Kell-Cellano (K-k), Lutheran (Lu), Lewis (Le), and Duffy (Fy). Therefore, there was need for a book summarizing all the recent findings. The authors of this book, who themselves have played a leading rôle in many of the newer discoveries, were eminently fitted for such a task, and their authoritative book on the subject will be welcomed by all interested in the field.

The book deals in detail with the serology and genetics of the various blood systems. Since, however, little space is devoted to the clinical aspects or to other applications such as anthropology, the book may be somewhat limited in its appeal. While it is indispensable for specialists in the field, physicians only incidentally interested in the subject will probably find it too difficult to meet their requirements, especially since little effort is made to cater to readers unfamiliar with the subject.

In the chapter on the A-B-O groups hardly any space is devoted to fundamentals, and the bulk of the discussion deals with such matters as calculation of gene frequencies, incomplete anti-A, and agglutinins of seeds. Perhaps too much space is devoted to highly controversial matters such as the so-called transtional forms or pleiades, and the so-called H substance.

The chapter on the M-N types contains an interesting discussion of the agglutinogen S, discovered by Walsh and Montgomery. Sanger and Race showed that factors M, N, and S form one system, the genetic behavior of which can be explained either by postulating a series of four allelic genes, *M*, *MS*, *N*, and *NS*, or by assuming the existence of tightly linked gene pairs, the latter corresponding to the theory sponsored by British workers in the case of the Rh-Hr types. The authors revive the question of a possible excess of type MN children from the mating MN × MN. However, as Wiener has shown, this is due in part to accidental statistical variations and in part to technical errors.

The next chapter, dealing with the P agglutinogen, contains some of the most recent observations on the distribution of this blood factor in various populations, including Germany, England, Egypt, and Czechoslovakia. Recent work is described confirming the original observations of Landsteiner and Levine indicating the existence of variants of the P agglutinogen. However, no reference is made to the work of Japanese investigators on the so-called agglutinogen Q, which is almost certainly a variant of the P agglutinogen.

The most extensive and important section of the book is the chapters dealing with the Rh-Hr types. The presentation here is hampered by the authors' adherence to the Fisher-

Race cross-over theory and C-D-E nomenclature in the face of knowledge which has accumulated since they were first formulated. Instead of revising their ideas to conform with the newer facts available, the authors force the facts so as to make them fit the theory. For example, the claims regarding the existence of antisera which demonstrate the factor Hr_0(d) have been contested by Wiener. If this factor exists at all, the authors themselves have never carried out tests for it, their own work being limited to the factors, hr′(c) and hr″(e). Therefore, on this basis, there is no convincing evidence that every Rh agglutinogen must consist of three and only three elementary factors. In fact, in the case of the agglutinogen Rh_1^w one must postulate the presence of at least four factors, Rh_0(D), rh′(C), hr″(e), and $rh^w(C^w)$. The Fisher-Race theory is put to task in the addendum when a new rare Rh agglutinogen is described consisting of only a single elementary factor, Rh_0(D). The authors fail to point out that when Wiener carried out the original investigations on the heredity of the Rh types, he considered all possible methods of genetic transmission, namely, independent genes, linked genes, and multiple allelic genes. When statistical evidence excluded the possibility of separate genes, either independent or linked, for each of the Rh factors, Wiener adopted the theory of multiple alleles. Subsequently, Fisher re-introduced the concept of linked genes which was then taken up by Race and is presented almost exclusively in this book.

When it comes to the Rh-Hr nomenclature, the authors offer an unsatisfactory solution. Since for most purposes the C-D-E notations are too cumbersome, in such situations they use "shorthand" symbols, which are the notations used by Wiener in 1945. Thus, the authors and the readers are compelled to learn two systems of notations instead of one. Moreover, when using the "shorthand" symbols, it is unfortunate that the authors did not adopt the 1950 Wiener notations throughout, instead of adhering to the older 1945 notations. Finally, it is difficult to understand why in using the Wiener notations the authors failed to take advantage of the distinctive symbols for phenotypes and genotypes. For example, the use of the phenotype notations would have vastly simplified table 83.

In the section dealing with the serology of the Rh-Hr types, attempts to force the observations on the rh^w factor to fit the Fisher-Race theory lead the authors into a number of inconsistencies. For example, to explain why ordinary anti-rh′ (anti-C) serum clumps both Rh_1 and Rh_1^w blood, they postulate that such sera contain two antibodies, anti-$C+C^w$. However, it then becomes difficult to understand why the antibodies from such sera should be completely absorbed by both Rh_1 and Rh_1^w blood, or why a type rh individual, sensitized to type Rh_1 blood, should form anti-rh^w agglutinins.

The chapter on the technique of Rh testing is terse. The directions given are not sufficiently detailed for the average laboratory technician; however, as has already been pointed out, the authors evidently intended this book for the use of specialists.

In the next section of the book, the authors present chapters containing information nowhere else available dealing with the Lutheran, Kell-Cellano, Lewis, and Duffy factors. As they point out, when tests are made for all the blood factors known to date, as many as 29,952 different phenotype combinations are theoretically possible. Of particular interest is Grubb's discovery, confirmed by the authors of the book, showing the relationship between the Le^a agglutinogen and the capacity to secrete A-B-O group substances. Unfortunately, all the anti-Le sera available to date have been of relatively low titer, so that blood specimens are encountered which are difficult to classify. Therefore, the relationship between the two Le factors, Le^a and Le^b, is not entirely clear, and the authors leave open the problem as to the exact mode of inheritance. Perhaps one of the most interesting chapters in the book is the one dealing with the problem of identification of the blood grouping antibodies. In this chapter the authors discuss the fascinating problem presented by in-

stances of multiple sensitization and explain the methods used for solving such difficult problems.

The book closes with a short section discussing the clinical applications of the blood groups and a somewhat more extensive chapter dealing with the use of blood groups in problems of parentage and identity.

The authors have succeeded in attaining their object of presenting and summarizing the most recent discoveries in the field of blood grouping, and their book is highly recommended.

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L'Hérédité des Prédispositions Morbides

By RAYMOND TURPIN (Faculté de Medicine, Paris, France) Paris: Libraire Gallimard, 1951. Pp. 261, with 27 figures. 450 fr.

THIS paper-covered, pocket-sized volume, written for physicians by a pediatrician with an interest in medical genetics, presents the author's assessment of the role that heredity plays in determining human predispositions to tuberculosis, other infections, cancer, allergies and rheumatism. The first chapter reviews briefly the current status of genetical knowledge, and concludes with the statement that investigations on the genetics of diseases such as infections, cancers or allergies run into such difficulties that their results are for the most part liable to numerous objections. Although the author seems aware of many of these objections, and in some cases lists them, he does not, in this reviewer's opinion, always give them sufficient consideration when drawing his conclusions, the result being that the unwary reader may be led to view with undue optimism our knowledge of the genetics of disease.

Chapter II discusses the inheritance of resistance to various infectious diseases including diphtheria, scarlet fever, syphilis, poliomyelitis and typhoid fever. The author has obviously read widely in the field and has himself done a considerable amount of work in it. He introduces the chapter with a statement of the precautions that must be taken in order to get reliable results when working with animals, and warns that in humans one should be even more rigorous in the choice of examples. Nevertheless he presents little good evidence for his conclusion that differences in susceptibility depend on the hereditary constitution and cannot always be explained by differences in the risk of contaminations or immunization by sub-clinical infections. It is extremely difficult to prove that variations in disease incidence between different ethnic groups are not environmentally determined, and the occasional clustering of many cases of a disease within a family group is expected even if the disease is distributed at random.

A number of reports of infectious diseases occurring in one or both of twins are reviewed, in many of which the classification of zygosity is made by inadequate criteria, thus largely invalidating the data. The author seems aware of the difficulties involved in establishing whether twins are mono- or dizygous, but nevertheless draws conclusions about the hereditary factors in disease from twin-studies which are untrustworthy in this respect. A critical review of the relevant animal work on the genetics of resistance to infection concludes chapter II. In chapter III, on tuberculosis, the author is far more careful in drawing conclusions than in the preceding chapter, and concludes that the thesis which best accounts for the variability of tuberculosis is that which invokes non-hereditary, environmental factors, specific and non-specific, and hereditary factors "sans doute" (apparently translated

as "probably") recessive. Chapter IV, on cancer includes a review of the more important experimental work on cancer genetics and it is concluded among other things that "human cancer is not a hereditary disease in the Mendelian sense, but the predisposition to cancer is dominated by heredity" and (on the basis of studies on a regrettably small series of twins) that chromosomal heredity plays an important role in the determination of the site of the tumor, especially when it is in the digestive tract and, in the female, in the breast and genital organs. Cytoplasmic heredity is also thought to be involved in the origin of tumors of the breast and genital organs. In chapter V the author reviews the genetic studies of allergy and concludes (among other things) that more work is needed in this confused field. Chapter VI, on rheumatism, omits the important work of Wilson *et al.* on the genetics of rheumatic fever, and proposes, on very shaky grounds, that the arthritic predisposition is inherited as a single dominant factor.

There are a few errors in the interpretation of elementary genetic principles. For instance it is said of sex-influenced heredity "where the gene expresses itself in the simplex state in females, but only in the duplex state in males" that an affected male could be born only of an affected couple (p. 181). Readers accustomed to orthodox Mendelian symbolism may find such practices as the use of "c" to refer to a (hypothetical) recessive gene for cancer susceptibility and "N" to refer to the normal allele (p. 179), somewhat confusing. There is an author index, a list of chapter headings and sub-headings, and a Bibliography, which is "voluntarily limited to works which attract attention by their novelty or by the abundance of their documentation." Thus many of the works cited in the text do not appear in the Bibliography, making it difficult to check original sources.

In spite of these criticisms the reviewer feels that the author has done a creditable piece of work in presenting to the French medical world a review of the current state of genetical knowledge (or lack of it) concerning some of the more common human diseases, and, if due regard is paid to the author's words of warning, his book should fulfil the aim expressed in its introduction, that by an appreciation of the ground already covered, new avenues of approach may be indicated.

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Die Konstitutionslehre von Carl Gustav Carus mit besonderer Berücksichtigung seiner Physiognomik

By Gerhard Kloos (Dozent, Psychiatrische und Nervenklinik, Universität Kiel, Germany). Basel: S. Karger Verlag, 1951. (Published also as Fasc. 90 of *Bibliotheca* (*Psychiatrica et Neurologica*). Pp. 112, with 14 figures. Swiss francs 8.—

Carus (1789–1869) was a German philosopher, anthropologist, physiologist, physician and artist who was particularly interested in physiognomy. It is remarkable how much he knew or surmised about the relations between body build in its various details and psychologic features characterizing an individual's personality. This booklet is of interest to the medico-historian rather than to the geneticist.

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BIBLIOGRAPHY OF HUMAN GENETICS

THIS section, prepared by the Editor in collaboration with Dr. R. H. Post, continues the list of current research articles and books of special interest to students of human heredity, which was started with the first issue of Volume I, covering the year 1949. The present list includes publications issued in 1950 (Part 5) and 1951 (Part 1). For further information regarding the organization of the Bibliography, see Parts 3 and 4 of the 1950 list published in the two earlier issues of the current volume. The numbers [3] and [4] following entries in the present list refer to these same two lists, where authors' addresses may be found.

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